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Title of Proposal: Evaluation of mHealth strategies to optimize adherence and efficacy of PMTCT/ART
Dates: 01/04/2014 – 31/03/2019

5) SUMMARY

In 2013, WHO recommended that all HIV-infected pregnant women receive lifelong antiretroviral therapy (ART) for prevention of mother-to-child transmission (PMTCT-ART) (formerly Option B+). This approach provides treatment benefits for women, preventive benefits for their infants and sexual partners, and implementation advantages. However, there are valid concerns about risks of this approach if maternal retention in care or adherence falters. PMTCT programs have demonstrated remarkable flexibility to incorporate new HIV-specific counseling, testing and educational messages in maternal child health (MCH) clinics. PMTCT programs now need to add adherence and retention support for all women initiating lifelong ART in settings where health care workers are already overburdened.

mHealth (Mobile Health) SMS (short message system) messaging is an evidence-based intervention that has been shown to significantly decrease treatment failure in adult ART treatment programs in Africa and may provide an inexpensive, feasible approach to enhance PMTCT-ART outcomes while supplementing rather than adding to provider workload. Our overarching hypothesis is that investment in mHealth for retention and adherence in PMTCT-ART will provide cost-effective benefit in sustaining antiretroviral regimen efficacy and durability.

We have collaborated with the University of Washington (UW) Department of Computer Science and Engineering (CSE) along with Kenyan telecommunication providers to develop a hybrid messaging system that includes both 1.) unidirectional automated yet personalized SMS messaging and 2.) innovative bidirectional SMS messaging. This system is currently under study in MCH clinics in Kenya. In qualitative research, women in Kenya have expressed a strong desire for mHealth support to provide additional education, counseling and reminders to supplement counseling by health workers. We hypothesize that mHealth strategies will improve PMTCT-ART maternal and infant outcomes. We also posit that both unidirectional and bidirectional SMS approaches will be cost-effective, and that bidirectional SMS may be superior to unidirectional SMS in improving both retention and adherence as well as maternal and infant outcomes.

We propose a 3-arm randomized trial comparing the effects of unidirectional SMS (ie: “push” messaging to participant) vs. bidirectional SMS dialogue between participant and provider vs. control (no SMS) among HIV-infected Kenyan mothers in Kenyan PMTCT-ART programs. In AIM 1 we will compare trial arms for impact on maternal retention, adherence, virologic failure and resistance and infant HIV or HIV-free survival. In AIM 2, we will determine correlates of maternal loss to follow-up and virologic failure and correlates of infant HIV in the overall study and stratified by trial arm. In the bidirectional SMS arm, we will determine the rate of SMS interactivity, impact of critical time-points on messaging, and characteristics of high and low ‘interactors’. In AIM 3, we will determine cost-effectiveness of unidirectional and bidirectional SMS interventions. These data will contribute a potential scale-able strategy to improve PMTCT-ART as programs aspire to ‘virtual elimination’ of infant HIV.

6)

a) INTRODUCTION/ BACKGROUND

PMTCT-ART is being scaled up and requires long-term retention and adherence. Over the past decade, interventions for PMTCT have increased in complexity from single-dose nevirapine regimens to Option A/B/B+ to the most recent WHO 2013 guidelines advocating lifelong antiretroviral therapy (ART) for all pregnant women (formerly Option B+).

b) LITERATURE REVIEW

There has been some experience with implementing this PMTCT-ART approach, notably in Malawi and Mozambique. In Malawi, recent scale-up of PMTCT-ART was rapid (Figure 1a), with a 12-month postpartum retention of 77%; the majority of those not retained were lost to follow-up (Figure 1b) (1). With increasing momentum to attain 'virtual elimination' of MTCT (e-MTCT) by 2015, more women will be initiated on PMTCT-ART which contributes to decreased infant transmission and sexual transmission (2). Over 1.5 million pregnant women globally were estimated to require PMTCT in 2011(3).

Figure 1a. PMTCT-ART in Malawi(1)

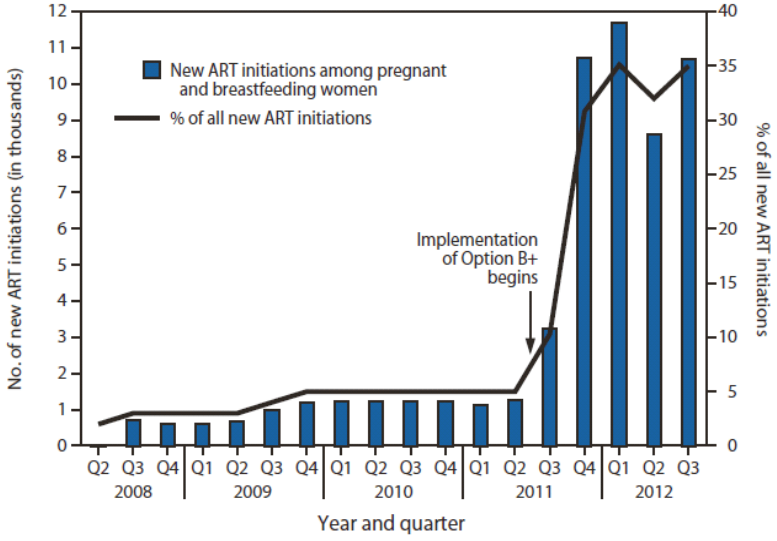
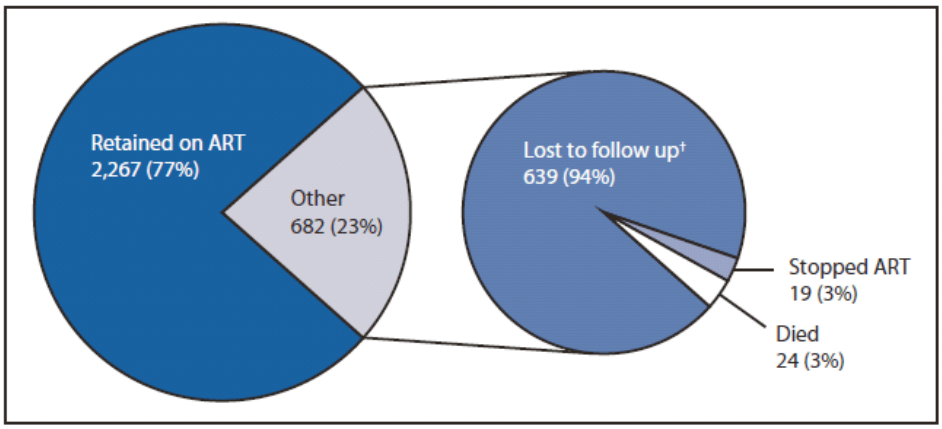


Figure 1b. Proportion lost to follow-up (Chimbwandira MMWR 2013)(1)



Retention in PMTCT Programs Declines throughout the PMTCT Cascade

In a systematic review of 33 studies from African ART programs in 2007, 2-year retention was estimated to be 61.6% ranging from 24% (worst scenario) to 77% (best scenario). Kenya average 2 year retention in this review was estimated at 66% (4). A review of 18 PMTCT studies noted loss to follow-up rates ranging from 19% to 89.4% whereas Kenyan loss to follow-up rates were ranged from 27% to 80% (5, 6). Initial efforts to enhance PMTCT coverage focused on HIV diagnosis, the first step to enter the PMTCT cascade – which was addressed by rapid, point-of-care, 'opt-out' testing (7). The next drop-off in the PMTCT cascade occurs in defining ART eligibility due to lags in obtaining CD4 results; this drop-off will be overcome by PMTCT-ART (8, 9). Post-ART retention is being estimated in programs implementing PMTCT-ART, however long-term data are lacking.

ART Adherence Declines Postpartum and May Compromise PTMCT-ART Effectiveness

Because of rapid viral replication in HIV, non-adherence in HIV leads to higher risk of disease progression and drug resistance (10). The contributors to non-adherence are multifactorial (5 dimensions) (11). In qualitative studies, reasons for non-adherence to ART included dissatisfaction with clinic, HIV denial, use of alternative medications, and side-effects, while adherence was facilitated by social support, ability to fit taking ART into their schedule, a belief that the regimen was of value, transportation to clinic, partner disclosure/violence and food availability (12-15). The relatively healthy status of mothers starting on ART may also pre-dispose them to non-adherence (16, 17). In a meta-analysis, postpartum adherence was significantly lower than during pregnancy (75.7% adherence in pregnancy vs. 53% postpartum, $p<0.005$) (18-20). Thus, in the context of PMTCT-ART a tailored approach that involves initial adherence counseling at ART initiation in pregnancy and 'booster' counseling messages when PMTCT ends may be necessary to sustain ART adherence and could be delivered via SMS messaging.

Interventions to Improve ART Adherence

There have been diverse approaches to improving ART adherence (21, 22). Intensive adherence counseling was associated with increased adherence and decreased viral failure (23). In a systematic review of ART adherence interventions, several interventions were found to be effective, including mobile phone SMS (24). However, for these interventions, effectiveness data was limited and long-term durability undefined. The US CDC guidelines combine pragmatic recommendations for improving ART adherence with educational/motivational approaches, some of which can be incorporated into an mHealth approach as shown in table 1 (25).

Table 1. US CDC guidelines to enhance ART adherence and potential applicability to mHealth (25)

US CDC guidelines for clinicians	Can be incorporated in PMTCT-ART mHealth
Multidisciplinary long-term adherence support team	Yes, include elements from pharmacy, clinic
Patient readiness	No-all women need ART promptly
Benefits of adherence	Yes
Decrease pill burden	Not applicable
Patient involved in decision-making re: regimen	Not applicable
Acknowledge difficulties; encourage disclosure of non-adherence	Yes bidirectional
Viral load to motivate	Possibly – currently no because VL not used in LMIC PMTCT; however, guidelines may shift to make this possible
Referrals to address factors leading to non-adherence	Yes
Education and tools	Yes
Manage side-effects of ART	Yes

PMTCT Counseling Quality and Quantity is Often Inadequate

PMTCT counselling already incorporates messages to help women cope with their new HIV diagnosis, disclosure to their partners, and PMTCT interventions. The high volume of patients and health care worker shortage makes it challenging to add a new message of lifelong ART adherence counseling. In an observed evaluation of PMTCT counseling, median post-test counseling was 38 minutes (26). Unlike prior short-course PMTCT models, PMTCT-ART programs will need to encourage ART adherence habits that persist lifelong and focus dually on child and maternal long-term outcomes. Thus, there is need to supplement PMTCT/MCH activities with ART-specific adherence interventions (Table 2).

Table 2. PMTCT Programs have Less Long-Term HIV Care Focus than HIV Treatment Programs

	PMTCT	HIV Treatment Programs
Clients	Young women, often no symptoms	Men and women suspect HIV risk, symptomatic
Health care workers serving clinic	MCH nurses – routine MCH and PMTCT	ART-dedicated health care workers
Counseling approach	Group pre-test, individual post-test	One-on-one, several adherence sessions
Counseling messages in clinic	Stop infant HIV	ART adherence lifelong
Health care worker focus	MCH, PMTCT, and HIV	HIV alone

Evidence that mHealth SMS Messages Enhance ART Adherence

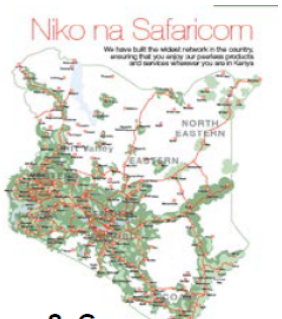


Figure 2. Coverage map for one Kenyan network

In Kenya, the number of mobile subscribers was reported at 29 million in 2012, in a national population of ~43 million (27, 28). In our preliminary studies in Kenya, pregnant and postpartum women report interest and perceive utility in receiving MCH SMS messages and are particularly interested in bidirectional dialogue options (29). A Cochrane review concluded that weekly SMS messages were beneficial for ART adherence and better than daily messages and that 'there is high quality evidence that SMS messages enhance ART adherence and viral suppression' (30-32). In an updated review of mHealth interventions for ART adherence presented at IAS 2013, 6 Randomized Controlled Trials (RCTs) and 2 observational studies were identified that

used SMS approaches (Table 3). However, the total number of studies is small and there are no data from PMTCT-ART programs.

Table 3: mHealth ART interventions published and ongoing

Study author, location, year	Number	Intervention	Study Design	Outcomes	Results or Status
Lester, WelTel Kenya, 2010 (30)	538 patients initiating ART	Bidirectional short SMS Weekly message required response in 48 hrs	RCT	Self-reported ART adherence (>95%), 6 & 12 mo VL suppression (<400 c/mL), 12 mo	RR for non-adherence 0.81 (95% CI O.69-0.94) RR for virologic failure 0.84 (95% CI 0.71-0.99)
Pop-Eleches, Kenya, 2011 (33)	431 patients initiating ART last 3 mo	4 unidirectional interventions (short wkly, short daily, long wkly, long daily)	RCT	Self-reported ART adherence >90% at 6 mo	Shortly weekly RR 0.78 (95% CI 0.68-0.89)
Mbuagbaw, Cameroon, CAMPS, 2012 (34)	200 patients in ART for at least 1 mo	Unidirectional "standard motivational" msg	RCT	Adherence by visual adherence score (VAS), self-report, pharmacy refill	No difference in any measure
Kimani, Kenya, registered 2010	~ 856 HIV+ pregnant women	Unidirectional SMS	RCT	Compliance with ANC, NVP in labor, EID	Ongoing
Ong'ech, Kenya, registered 2012	600 HIV+ pregnant women seeking ANC	Bidirectional "mobile communication with providers	Cohort	Proportion of women who complete PMTCT milestones to 6 wk postpartum	Ongoing
Palha, Mozambique SMSaude, registered 2013	HIV infected adults and HIV infected pregnant women	Unidirectional PMTCT SMS reminders, ART reminders	RCT with 2 different cohorts	Retention in ART	Clinical procedures completed

<u>Need For Further mHealth Research Including Optimizing mHealth Strategy, Cost-Effectiveness and Cost-Savings To Inform Programmatic Scale-Up</u>

PEPFAR and Ministries of Health (MOH) are in need of relevant effectiveness and programmatic cost data to inform scaling of mHealth interventions. The Kenya MOH has included mHealth interventions as part of its eMTCT priorities. However, there are still limited published mHealth evaluations in HIV. While studies have evaluated the role of differing frequency of messages, they have either used unidirectional or bidirectional messages but not compared these to each other. To date no study has demonstrated the level of SMS interactivity required to demonstrate optimal effectiveness or evaluated the additional cost and provider burden of this SMS intervention. Unidirectional messaging is less expensive and complex than bidirectional messaging but may have lower effectiveness.

7) RATIONALE

SMS Messaging has potential not only to educate but also engage women to adhere to PMTCT-ART without placing an additional burden on health care workers. This project leverages the innovation of mobile communications to sustainably increase ART adherence within PMTCT-ART. Personalized and dynamic messaging may be more effective in producing behavioral change (35). SMS interventions may be cost saving in avoiding treatment failure and cost-effective. Furthermore, evaluation of unidirectional informative SMS versus bidirectional interactive SMS in a health care setting is novel. Determining the optimal level of messaging interaction required for successful behavioral change is essential for development of large-scale mHealth strategies. While unidirectional SMS provides low-cost dissemination without additional interactions with health care workers, it may not engage women enough. In contrast, bidirectional SMS requires action from the message receiver and allows for exchange of questions and

concerns, which may enhance engagement and ultimately uptake of services; however, it is requires more interaction with health care workers than unidirectional SMS. This project will evaluate potential added benefit as well as expense and health care worker time for bidirectional messaging.

8) HYPOTHESIS & STUDY QUESTIONS:

Our overarching hypothesis is that investment in mHealth technologies for PMTCT-ART will yield cost-effective, long-term benefits by maximizing impact and durability of ART. This hypothesis is motivated both by emerging adherence literature, and specific ART adherence RCTs in Kenya, in which SMS interventions significantly decreased treatment failure in adult HIV Treatment programs and increased return for early infant HIV detection in PMTCT programs. Building on our qualitative research among pregnant women in Kenya that revealed a desire for mHealth SMS messages and dialogue, we developed an interactive mHealth system (Mobile WACh) in collaboration with the UW Department of Computer Science and Engineering (29). This system, now in use in Kenya, can be readily adapted to deliver and receive messages regarding PMTCT-ART. We propose to conduct a 3-armed RCT to determine the impact of mHealth SMS strategies on adherence, retention, and outcomes in PMTCT-ART programs with the following specific AIMS:

9) OBJECTIVES

a) BROAD OBJECTIVES

The broad objective of this study is to determine the impact of mHealth SMS strategies on adherence, retention, and outcomes in PMTCT-ART programs.

b) SPECIFIC OBJECTIVES

AIM 1: To compare mother-infant pairs receiving systematic, tailored unidirectional SMS messaging vs. bidirectional SMS dialogue vs. control (no SMS) for outcomes measured during 2-year postpartum follow-up, including:

a) Maternal retention in care, ART refills, virologic treatment failure, and ART drug resistance

b) Infant HIV infection and HIV-free survival at 6 weeks, 6 months and 24 months

c) Maternal perceptions of acceptability, utility and strengths/weaknesses of unidirectional and bidirectional SMS

Hypothesis 1: Long-term retention, ART adherence, and maternal/infant outcomes will be enhanced by SMS. Mothers will endorse SMS approaches, preferring bidirectional messaging dialogue.

AIM 2: To determine correlates of maternal treatment failure (loss to follow-up, virologic failure, or ART resistance) and correlates of infant HIV infection in the cohort overall and stratified by arm, and characterize SMS interactions among women in the bidirectional SMS arm, including frequency of and changes in interactivity over time, relationship to pivotal time-points (delivery, cessation of breastfeeding, transfer of care to ART clinic), characteristics of high and low 'interactors', and topics motivating interactions.

Hypothesis 2: Lack of disclosure to partner, distance to clinic, and poor understanding of need for lifelong ART, will be associated with maternal treatment failure. Interaction frequency with bidirectional SMS will decline over time, and 'higher-interactors' will be younger, primigravida, and more educated.

AIM 3: To assess the cost-effectiveness of unidirectional SMS and bidirectional SMS interactions: a) Estimate net cost savings realized through the reduction of treatment failure and drug resistance. b) Estimate incremental cost-effectiveness in improving infant and maternal health outcomes.

Hypothesis 3: Both interventions will be cost saving and cost-effective; bidirectional SMS will be more cost-effective.

10) STUDY DESIGN AND METHODOLOGY

This is mixed methods study that includes qualitative components and a triple-arm, non-blinded RCT. The study has 3 phases:

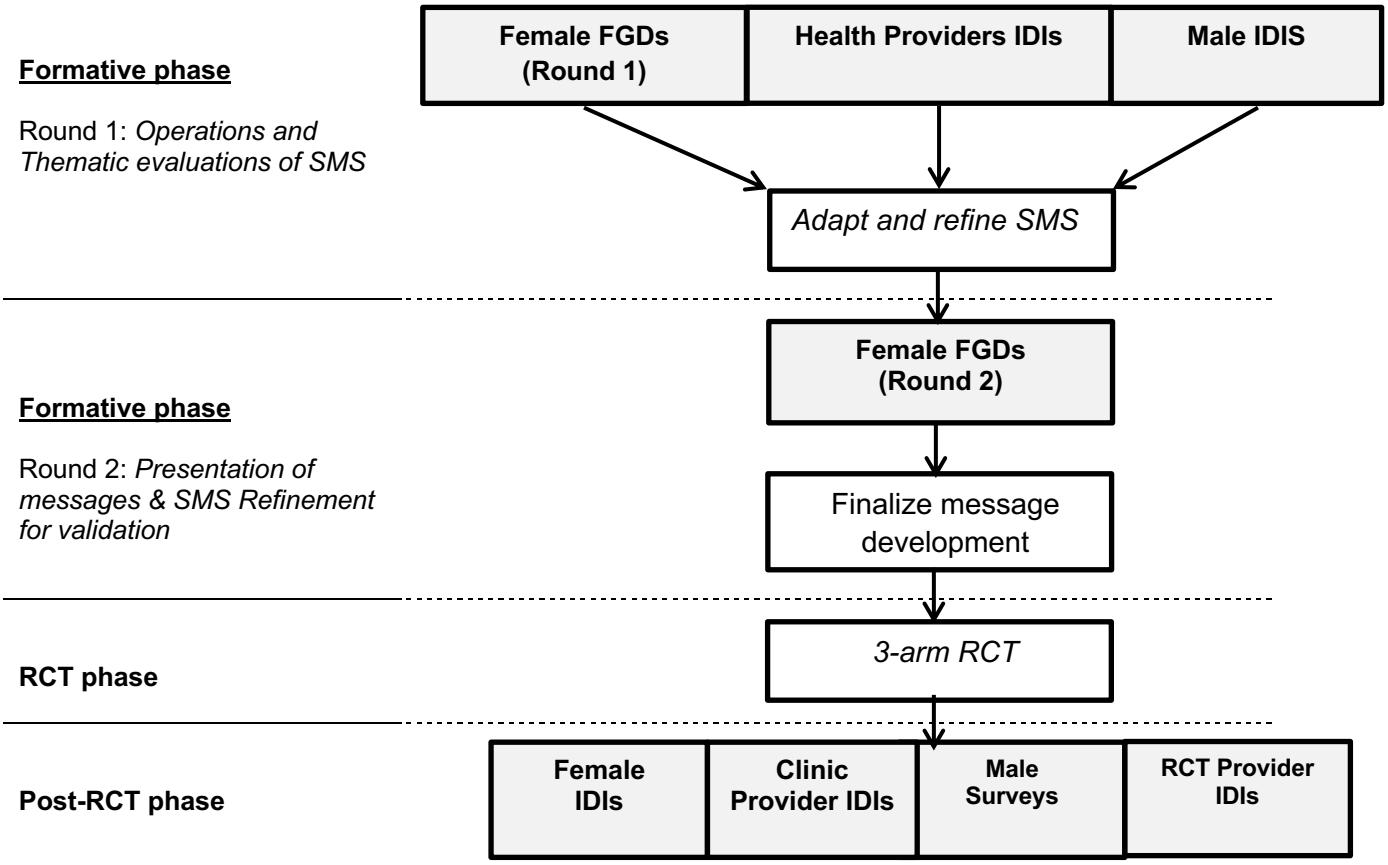
- **Phase 1**: Formative phase with 2 rounds of female focus group discussions (FGDs), male in-depth interviews (IDIs) and health provider IDIs.
- Phase 2: RCT phase, a triple-arm RCT to evaluate two mHealth interventions designed to enhance long-term ART adherence in PMTCT-ART programs.
- Phase 3: Post-RCT phase, IDIs with RCT participants, clinic health providers, study nurses, and surveys with male partners of RCT participants.

a) STUDY AREA DESCRIPTION:

The proposed study will be conducted at six sites in Kenya: the Ahero sub-District Hospital, Bondo District Hospital, Siaya County Referral Hospital and Rachuonyo sub-County Hospital in Nyanza region and Mathare North City Council Clinic and Riruta Health Centre in Nairobi. These are all high volume government-run public health facilities which serve low- to middle-income rural (Bondo, Ahero, Siaya and Rachuonyo) and peri-urban (Mathare and Riruta) populations. From our previous studies at these sites, HIV seroprevalence among pregnant women is 15% at Mathare and 19% Ahero and Bondo. These four sites provide a wide range of ANC, postnatal care, and HIV services in their catchment areas.

An overview of all study procedures is shown in Figure 3.

Figure 3: Overview of study procedures



PHASE 1: FORMATIVE PHASE

a) STUDY DESIGN

FGDs and IDIs

FGDs are an effective technique to compare experiences and views between participants, and gather the "group effect", rather than relying on individual data (36).They also provide a breadth and depth of information regarding social norms such as acceptability, which is imperative for successful interventions. IDIs are useful because they provide much more detailed information than what is available through other data collection methods, such as surveys. They may also provide a more relaxed atmosphere in which to collect information and people may feel more comfortable having a conversation (37). IDIs and FGDs will be conducted by a Kenyan team trained in qualitative research methods and will probe for further elaboration on relevant content from the semi-structured FGD guide. Study investigators experienced in qualitative methods, Dr. John Kinuthia (site-PI) and Dr. Gabrielle O'Malley (co-investigator), have reviewed topic guides for content validity and cultural relevance.

b) STUDY POPULATIONS

The formative phase of the study will include three different populations and study designs: female FGDs, male IDIs, and health care provider IDIs. The study participants will be drawn from peri-urban (Mathare, Nairobi) and rural (Ahero and Bondo, Nyanza) regions of Kenya.

Female FGDs:
The study population will comprise HIV-infected pregnant women seeking antenatal care services at three public facilities in Nairobi and Nyanza regions. Women are primarily attended to by health providers: nurses, clinical officers, pharmacists, peer counselors, and mothers-to-mothers (M2M) counselors. The source population is drawn from both rural (Ahero and Bondo) and peri-urban (Mathare) areas, diverse in ethnicity, and of generally low socioeconomic status. Women who are HIV-infected will be offered participation in the study.

The overall objective of the female FGDs is to narrow/refine themes and wording of SMS messages for the RCT. We will conduct 2 rounds of FGDs with women prior to initiating the RCT.

The goals of Round 1 FGDs are to:

1.) Determine the acceptability of potential pre-developed SMS content themes
2.) Elicit ideas for additional messaging themes
3.) Present and evaluate pre-developed messages to determine comprehension, acceptability, and ideas for refinement.

The pre-developed SMS topics will include: pregnancy, antenatal and postpartum care, medication and clinic visit reminders, infant care including feeding practices and general encouragement messaging. Utilizing data from Round 1, the second round of FGDs will be used to refine and finalize SMS messages for the RCT.

Table 4: Composition of female FGD participants with varied PMTCT/ART experience in each FGD

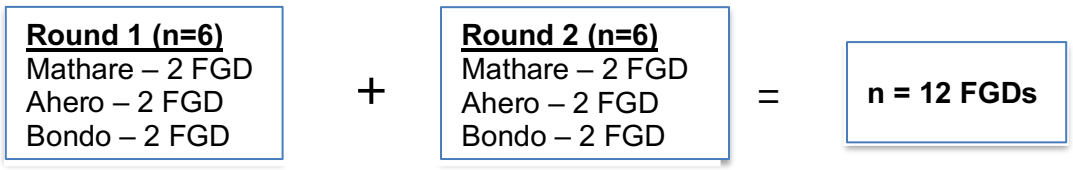
	PMTCT experience[1]	ART experience[1]	No-PMTCT /ART experience[1]	Total[1]
Pregnant HIV+ women	2	2	2	
Postpartum HIV+ women	3	3	3	
Total per category	5	5	5	**15**

[1]Maximum number of women

We will purposively sample women based on pregnancy/postpartum status and PMTCT/ART experience as indicated in Table 4 above until we have up to 15 women enrolled in each FGD and the desired population.

For each round of FGDs, we will conduct 6 FGDs (2 FGDs per clinic) for a total of 12 FGDs combined in Rounds 1 and 2 (Figure 4). Thus, we will recruit a total of 180 women for the FGDs.

Figure 4: Focus groups by study site



Male IDIs: IDIs will be conducted with a total of 30 men who have HIV-infected partners to:

- Obtain additional information to guide SMS intervention development and distribution

- Obtain feedback on sample SMS messages
- Explore desirability and feasibility of involving male partners
- Understand potential concerns of male partners that could be addressed by modifying SMS messages

We will include two groups of men for IDIs: HIV infected men with a current infected partner recruited from HIV clinics where the men attend care and HIV uninfected men who are referred to the study from their self disclosed partners who attend MCH clinics. HIV-infected men will be purposively sampled from CCCs. HIV-uninfected men will be referred to the study by women who have disclosed their HIV status to their partner and have known HIV-uninfected partners for potential participation in an IDI and survey administration.

Provider IDIs: We will conduct 30 Key Informant IDIs (10 per site). We will interview Nursing officer in charge, MCH nurses, clinical officers and pharmacists to determine how SMS messaging can be used to augment the current care being delivered in clinics. We will specifically explore challenges providers face in the care of HIV infected women and their views on how enhanced communications via SMS could address these challenges and improve retention and adherence. We will also engage peer counselors and mother-to-mother (M2M) counselors through IDIs to elicit their views of how SMS can work to improve adherence and retention. M2M are mothers living with HIV who are trained to provide health education and psychosocial support to other HIV-positive mothers on PMTCT. We will specifically explore how this technology could be useful for their responsibilities (psychosocial support, counseling, assisting client on enrolment in care, patient tracing) and elicit advice regarding sensitive issues around confidentiality and other concerns when communicating with HIV infected women, and suggestions for enhancing the intervention.

Table 5: Layout of Phase I (formative) procedures, study populations, and eligibility

	FORMATIVE PHASE		
Population & maximum sample size	Women N=180 (15 per FGD)	Men N=30	Health providers N=30
Study procedures	FGDs, N=12 • 6 FGD x 2 rounds (2 FGD per clinics per round)	IDIs 10 in Mathare 10 in Ahero 10 in Bondo	Key Informant IDIs • 10 per site
Topic	Additional strategies and themes for message content, share SMS content for feedback and refinement	Additional adherence strategies, personal experiences, assess desired degree of involvement	Current counseling messages, duration of HIV counseling, messages they lack time to deliver, SMS content to consider adding, concerns about SMS
Recruitment	From ANC, MCH, and CCC	From ANC, MCH and CCC	ANC, MCH

Eligibility	• HIV-infected women > 14 years • PMTCT or ART naïve or experienced • Women should be either: ▪ ≤36 weeks gestation or ▪ Have HIV-uninfected child ≤2 years (and HIV infected when pregnant with the child), • Daily access to mobile phone • Willing to receive SMS • Literacy not required if women have access to a partner/family member whom she would be comfortable to have read her the messages • Willing to provide informed consent	• Have HIV-infected female partner with a child (≤2years old) OR who is accessing antenatal care or postnatal care services • Referred by female partner or attending CCC alone. • Willing to provide informed consent	• Directly involved with care of HIV-infected pregnant women and HIV-exposed infants • Willing to provide informed consent

c) RECRUITMENT PROCEDURES

Female FGD: A study staff member will approach HIV infected women in ANC, MCH clinics and CCC to briefly describe the purpose of the FGDs and invite interested women to be assessed for eligibility and participation. It will be emphasized that participation is completely voluntary. Women will be notified that by participating in FGDs with other HIV infected women, they are self-disclosing their HIV status and confidentiality cannot be maintained within the FGD due to the nature of FGDs. It is common practice for these women to meet in a group during ANC and MCH care. Women who are uncomfortable having group discussions with other HIV-infected women in the FGD will be told that the FGD is not a good fit for them. However, we will emphasize the need for confidentiality outside of the FGD for all study participants. Eligible participants will be given a date to return for FGD. Participants will undergo the informed consent process prior to FGD.

Male IDIs: HIV-infected women from ANC, MCH and CCC will be approached by study staff about potential participation of their male partners and informed about the Male IDIs. They will be asked whether they have disclosed their HIV status to assess study eligibility. Women who have disclosed their HIV status to their partners, will be requested to refer their male partners for IDIs. For those women interested in asking their partners to participate, we will provide them a "study clinic referral form" (Male Partner IDI Pre RCT Referral Form) to give their partner. A study staff will also approach partnered male patients, in CCC, previously identified by clinic staff, and describe the purpose of the IDIs and invite interested men for eligibility assessment and participation. Study staff will work with clinic staff to identify men who have visited CCC alone. Once male participants present for enrollment, they will be given more information on the study. It will be emphasized that participation is completely voluntary. If interested in participation, they will get an appointment for an IDI. Eligible participants will undergo the informed consent process. IDIs will occur immediately after the consent process.

Provider IDIs: Pre-RCT, key informant health providers will be approached by study staff who will describe the purpose of IDIs and invite health providers to participate. Health providers consist of clinical staff serving HIV-infected pregnant women (Nursing officer in-charge, nurses, clinical officers, pharmacist) and non-clinical staff (peer counselors and Mothers to Mothers (M2M) counselors). We will emphasize that IDIs are completely voluntary. Those who

are willing and able to participate will get an appointment for IDIs. Eligible participants will undergo the informed consent process. IDIs will occur immediately after the consent process.

d) DATA COLLECTION PROCEDURES (clinical and non-clinical, field, data collection instruments)

Both FGDs and IDIs will be performed in a private area. Participants will meet a trained interviewer or moderator who will ask questions and take notes. Consent will be obtained from participants to take notes and audio record the discussion. Socio-demographic information from participants will be documented in separate forms. Socio-demographic information that will be captured include: age, marital status, education level, employment, number of children, and partner HIV status as shown in the participant survey (included in with the IDI and FGD guides).

The interviewer/moderator will describe procedures and norms for discussion and participation. Participants will be given a chance to ask questions regarding procedures prior to the discussion.

Discussions will be guided by the interviewer or moderator using a discussion guide (attached). Prior to FGD, the moderator will stress the importance of maintaining confidentiality within the group. Participants will receive unique identification numbers and will not be addressed by their real names so as to maintain confidentiality. Topics that generate the most discussion, participant attitudes, non-verbal gestures, and interaction dynamics among group members will be documented by the moderators. Discussions will be conducted in English, Kiswahili, or Luo depending on participant preferences. Thereafter, notes will be compared to audio-recordings to fill in missing information and transcribed to English (if necessary). Transcribed data will be de-identified. Tape-recorded discussions will be destroyed no later than 3 years after conducting the FGD or IDI.

Participants will be provided refreshments and Ksh. 300 to compensate for their time and transportation expenses to participate in the study. We will provide this monetary compensation to each participant at the conclusion of each discussion.

e) DATA COLLECTION INSTRUMENTS

Paper copies of data collection tools for surveys accompanying IDIs and FGDs are submitted with this application for human subjects review.

PHASE 2: RANDOMIZED CONTROLLED TRIAL

a) STUDY DESIGN

We will enroll and randomize 825 HIV-infected pregnant women (275 per arm) in a triple-arm, non-blinded RCT. We will enroll and randomize women to unidirectional SMS, bidirectional SMS, or control during pregnancy and measure maternal retention in care, ART refills, virologic treatment failure, and drug resistance during a 2-year postpartum follow-up period (Aim 1a). We will also assess the effect of the interventions on infant HIV infection and HIV-free survival (Aim 1b).

SMS MESSAGE DEVELOPMENT AND DELIVERY

SMS messages will be designed using an iterative process that integrates findings from a preliminary SMS intervention (Mobile WACh) and formative FGDs and IDIs. This process will incorporate the constructs of Theory of Planned Behavior and Social Cognitive Theory in understanding drivers of behavior change and direct appropriate message development (38, 39)

SMS messages will provide tailored and actionable education, counseling, and reminders specific to pregnancy/postpartum status. Messages will be based on Focused Antenatal Care WHO guidelines and the recently adopted Kenyan maternal child health handbook as well as the Kenyan HIV guidelines (40-42).

Messages will be tailored to antenatal/postpartum timing, new vs. prior ART, maternal age group (adolescent or adult), and HIV disclosure to partner. SMS messages will be translated into local dialects. Messages will be tested in English, Kiswahili and Luo.

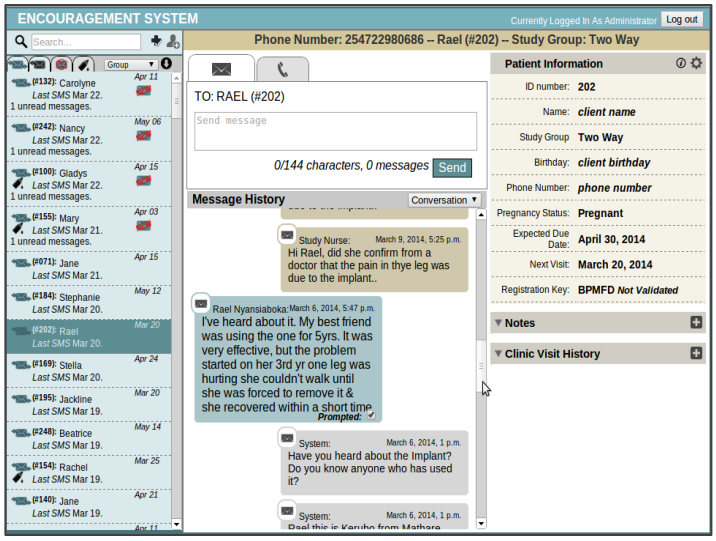
Informative Unidirectional SMS Messaging: SMS will be delivered once weekly to participants. The message will act both as a reminder and cue to action. Pre-programmed messages will be delivered at times and in languages based on patient preferences. The service will be provided free of charge.

Interactive Bidirectional SMS Messaging: SMS will be delivered once weekly to participants. The diagram (Figure 5) on the left shows a screen shot of Mobile WACh SMS interface with dummy messages and data. Pre-programmed messages will be delivered at times and in languages based on patient preferences. They will include a question soliciting a response from the participant. If no response is received, the participant will receive a “check-in” SMS after failing to respond for 2 weeks. The “check-in SMS” will ask if participant is receiving SMS and if she is well. If no response is received from the participant, no further “check-in SMS” will be sent. However, she will continue to receive standard weekly SMS. Participants in the bidirectional messaging group will also have the capability of texting spontaneously to the system. Interactive SMS communication will be responded to and managed by the study nurse at each site.

We have partnered with a local premium rate service provider (PRSP), Shujaa Solutions, to provide SMS dialogue free of charge to participants.

In this RCT, bidirectional SMS dialogue will be managed by study nurses and standard operating procedures (SOPs) will be developed for standardizing responses to the questions received. Thus, study nurses will follow national guidelines and local practice standards to respond. The process will be adaptive as new scenarios unfold with dialogue –a new question not addressed by the SOPs will be discussed by study team and SOP developed if it is a question likely to be encountered repeatedly. Weekly review of the log of SMS narrative will enable standardization, quality assurance, and understanding women’s use of the system and their level of interaction it. Issues to be examined within the bidirectional intervention arm include ability to standardize messaging, time demands, and time-cost.

Figure 5: Screen-shot of mobile WACH SMS interface with drafted data



Controls: The control arm will receive standard education and counseling provided in ANC.

Phone Calls: All participants will receive a phone call at 1 month and 1 year after the estimated delivery date (EDD). The purpose of this phone call is to obtain delivery information and health status information for those women who have been lost to follow up. We will also conduct a final phone call at 2 years postpartum along with the home visit. The purpose of the final phone call is to set up the home visit. If the patient prefers not to have a home visit, we will attempt to collect final data follow-up during this phone call.

Figure 6: Map of timeline of message themes that will be sent out to women

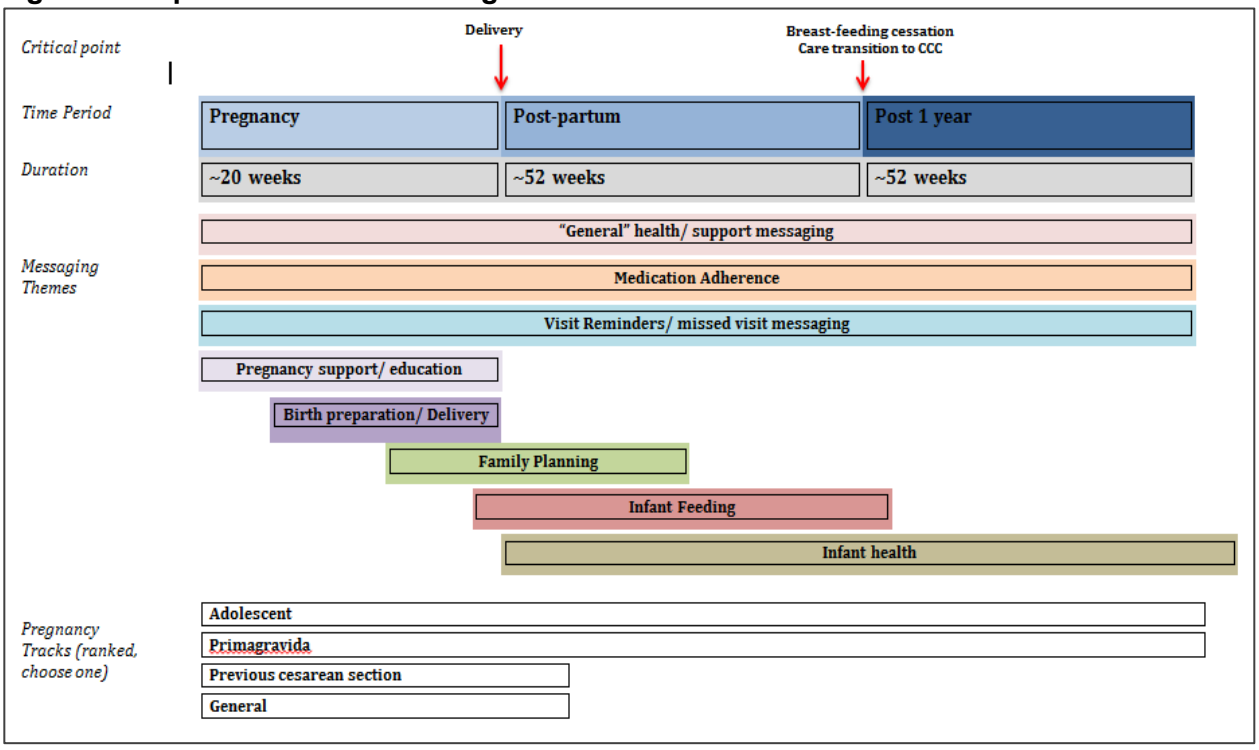


Figure 7: Display of sample SMS messages by themes

Examples of one-way messaging

Examples of two-way messaging with questions

b) STUDY POPULATION

The study population will comprise HIV-infected pregnant women seeking antenatal care services at three public facilities in Nairobi and Nyanza regions. The source population is drawn from both rural (Ahero, Bondo, Siaya and Rachuonyo) and peri-urban (Mathare and Riruta) areas, diverse in ethnicity, and of generally low socioeconomic status. Women who are HIV-infected will be offered participation in the study. HIV care and treatment in these sites is supported by the MOH and two non-governmental organizations, International Center for AIDS Care and Treatment

Programs (ICAP) and AIDS, Population and Health Integrated Assistance (APHIA-plus). Based on ANC attendance and HIV prevalence data, we anticipate 20 women per month will be eligible for participation at Ahero, Bondo, Rachuonyo and Riruta and 35 women per month at Mathare and Siaya.

c) SAMPLE SIZE DETERMINATION AND FORMULAS USED

RCT sample size

Table 6. Sample size for unidirectional or bidirectional SMS vs. control or unidirectional vs. bidirectional; gray shaded shows cells with sufficient power and n is number per arm

Intervention	Prevalence of outcome	Control			
		70%	**75%**	**80%**	**85%**
	85%	120	250	302	-
	90%	62	100	199	686
	95%	35	49	75	140

Sample Size Estimates Assuming alpha=5%, power=80%, 2-sided test, 1:1:1 allocation ratio, with a sample size of 275 per arm, we would have sufficient power to detect an increase in retention or increase in virologic suppression (inverse of virologic failure) from 75% (control) to ≥85%, allowing for 10% attrition; we will also be able to detect an increase in ARV adherence from 85% to ≥95% (Table 6). Thus, the total cohort sample is 825 women. We could see a difference from 75% to 85% between control and unidirectional SMS and additionally detect a difference between uni- and bidirectional SMS (85% to 95%). Similarly, we will have sufficient power to detect an increase in infant HIV-free survival from 85% to ≥95%.

d) RECRUITMENT PROCEDURES

MCH nurses or other clinic staff will introduce the study and refer interested women to the study clinic after the ANC visit. (please see attached recruitment scripts) Study nurses will inform women about the study, answer any questions they have and invite women to participate in eligibility screening for the RCT. It will be emphasized that their participation would be completely voluntary and would not in any way affect their access to ANC, HIV, postnatal, or infant care services. In order to capture the proportion of women referred who meet our eligibility criteria and are interested in participating, a screening questionnaire will be used to collect data on eligibility. The screening questionnaire (attached) records no personally identifiable information. Oral consent will be obtained for participation of interested women in the screening phase. Eligible women will be invited to participate in the RCT. Those eligible women who decide not to participate will be asked for their reasons for non-participation, and these will be recorded in the screening questionnaire.

Eligibility: HIV- infected pregnant women will be recruited for the study. Women will be eligible if they are ARV naive, previously received ART or are currently on ART, have access to cell phone, ≥ 14 years and < 36 week gestation (Table 7).

To enhance generalizability, literacy will not be required if women have access to a partner or family member whom she would be comfortable to have read her the messages. This approach was developed in consultation with mothers in Kenya, who felt that involving their partner was acceptable and may engage more support. Eligible women will undergo screening, the informed consent process, and be randomized. Participants will be asked their preferences for message delivery including language, days of the week and time of the day.

Table 7: Layout of Phase 2 (RCT) procedures, study populations, and eligibility

	RCT PHASE
	Females
Population & maximum sample size	Women N=825
Study procedures	3-arm RCT
Topic	Compare unidirectional, bidirectional and no SMS
Recruitment	ANC
Eligibility	• HIV-infected women ≥ 14 years • Daily access to mobile phone and willing to receive SMS • Literacy not required if women have access to a partner/family member whom she would be comfortable to have read her the messages. • Expected continued residence in study area for the study duration • Willing to provide informed consent • Not enrolled in other studies

e) RANDOMIZATION PROCEDURES

Participants will be randomized to: 1) Simple unidirectional SMS messaging, 2) Interactive bidirectional SMS dialogue, and 3) Control, using 1:1:1 allocation. A computer-generated randomization list will be generated using random block sizes in STATA. The allocation codes will then be put in sequentially numbered sealed envelopes. Participants and study will be un-blinded to randomization arms.

f) DATA COLLECTION PROCEDURES

Women will be followed during pregnancy and for two years postpartum; all clinical care will be managed through the existing MCH and CCC infrastructure. Because the study aims to determine mHealth benefits in a routine clinic setting, specific ANC/PMTCT/HIV services will be delivered by the MOH programs with minimal clinic interactions with study personnel. The study team will abstract data regarding clinic attendance, pill refills, infant health and infant HIV status from the PMTCT program registry, labor and delivery ward, pharmacy and peer counselors registers. Viral load and infant HIV testing results will be abstracted from the national electronic viral load dashboard. We will make check-in calls to all participants regardless of study arm at 1 month and 1 year post-EDD. This will be done to ascertain mother's delivery status, infant status, and that phone number is up to date. Check-in calls will be done by data management teams and will call the participants contacts if they fail to reach study participant.

The study visit schedule will be: enrollment (any time in pregnancy), 6 weeks postpartum, then every 6 months up to 24 months. At each visit a standardized questionnaire will be administered using a tablet-based system (Open Data Kit, ODK) developed by the UW Department of

Computer Science and Engineering collaborators. Between study visits, data will be obtained from patient records in order to inform personalized, dynamic messaging. For example, if a participant in one of the intervention arms misses an appointment an appropriate SMS will be sent to address this absence and encourage the participant to reschedule. If a participant in the bidirectional arm does not respond after receiving two weekly messages, she will receive a check-in message asking if she is receiving messages. The study nurse will review clinical records daily to check for missed appointments, deliveries, clinic visits, infant immunizations, or any clinic contact from study participants. Delivery information from women will be obtained at 6 weeks postpartum and data abstracted from records at MCH-linked maternity centers. Follow-up will continue until 24 months postpartum.

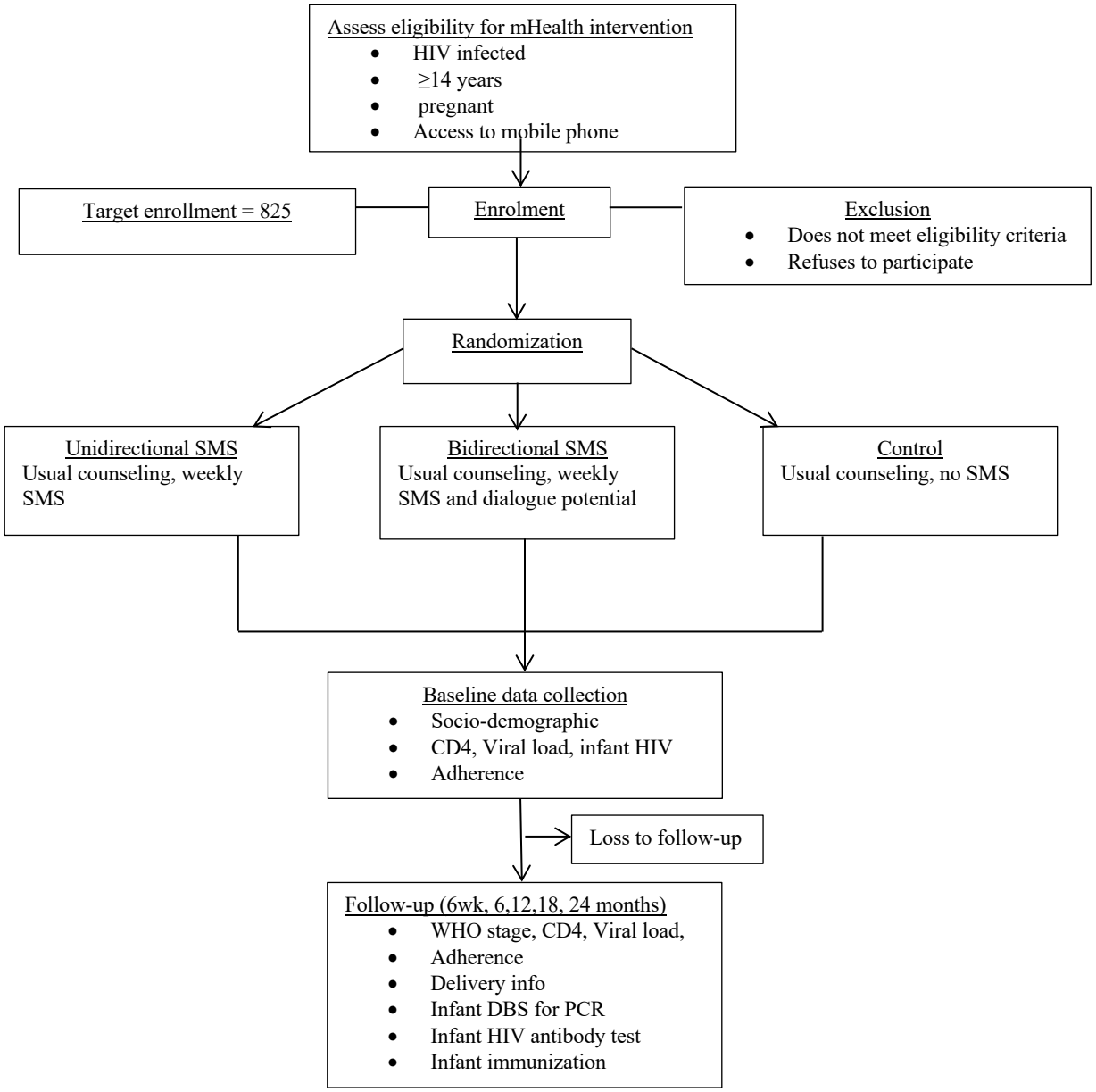
In order to ensure completeness of clinic record abstraction for the study period, photographs will be taken at study exit of participants' CCC cards. All identifiable information, including name, date of birth, CCC number, ANC number and address will be covered with paper, and the record will be labeled with the participant's study ID only. Photographs will be transferred to a password-protected computer and secure server within 1 day of the photograph being taken and permanently deleted from the device used to capture the image. At the final study visit, in order to verify the data collected during abstraction, we will measure the height, weight, and mid-upper arm circumference of participants and their infants.

We will collect 14 ml maternal plasma samples for CD4 count, HIV viral load, and suspected drug resistance testing for mothers and 0.5 ml for HIV DNA DBS and HIV antibody testing for infants at all study visits. SOPs will be used to guide venipuncture procedure. The study will obtain viral loads for all participants. However, if the Kenyan MOH incorporates routine HIV viral load testing on a national scale and the testing intervals are similar to those proposed by the study, we will utilize viral load results from the standard of care rather than repeat viral loads.

While retention procedures will be minimized in order to avoid contamination of the intervention on retention outcomes, we will obtain phone numbers of contacts and conduct home visits after enrollment to ascertain locator information. This information will be used at the end of the RCT to conduct home visits to re-establish contact for participants who failed to return for appointments and are lost to follow up in order to ascertain 24-month postpartum outcomes. Participants who are not able to attend the 24-month visit at the clinic will have their 24-month visit procedures conducted at the home visit. Figure 6 illustrates study flow from enrollment to follow up.

In addition to collecting data from study participants during the trial, a facility survey will be conducted with a facility manager at each study site to collect information regarding facility characteristics, Option B+ implementation, human resources, service disruption and service management. The purpose is to identify whether facility-level factors associated with participant clinical outcomes. No human-subject data will be collected.

Figure 6: Consolidated Standards of Reporting Trials-CONSORT diagram of RCT design



We will collect patient information at baseline and follow-up visits using:

- Participant surveys: demographics, clinical and sexual history, family planning, disclosure, medication adherence, experience with SMS and technology, intimate partner violence, and depression
- Medical and pharmacy record extraction forms will be completed by data teams: delivery information, infant immunizations, maternal health, infant health, medication adherence, lab forms, pharmacy data, maternal mortality, and infant mortality.

- Viral load and infant HIV test results will be abstracted from the national electronic VL dashboard.

g) VARIABLES: Outcomes, indicators, and source documents

Table 8: RCT Outcomes

Primary Outcomes	Indicator	Source
Retention	Seen at scheduled visits	PMTCT register for scheduled visits
Drug Adherence	Number/ expected	Self-report , pharmacy 6 wk, 6, 12, 18, 24 mos
Maternal viral suppression	HIV RNA	Maternal blood at 6 wk, 6, 12, 18, 24 mos
Maternal drug resistance	OLA	Resistance assay in mothers with viral failure
Infant HIV	HIV testing: DNA on DBS and antibody	HEI register week 6, infant specimens
Infant HIV-free survival	HIV DNA, antibody and mortality	HEI register week 6, Infant specimens 6, 12, 18, 24 mos; verbal autopsy
Maternal perceptions of intervention	Standardized questions	At study visits, subset FGD
Cost-effectiveness, cost-savings	Cost/time questions	Interview, clinic
Selected Secondary Outcomes		
Postpartum contraception	Use of effective contraception	MCH card, CRF
Exclusive breastfeeding	Ever, duration	CRF
Infant mortality	Death during follow-up	CRF, verbal autopsy

Notes: MCH: Maternal-Child Health; CRF: case report form

Outcomes

A summary of proposed outcomes is provided above in Table 8 (above). Retention is a primary outcome in this RCT, thus we seek to observe the effect of the intervention on retention rather than using comprehensive strategies to optimize it. To ascertain other outcomes, a relatively low intensity of study visits (6-monthly) has been designed; however, we are aware that this will compromise retention compared to our prior studies with >90% retention in which more frequent study visits facilitated retention. For all arms, we will not trace participants who do not attend clinic with home visits until study end, when we will conduct home visits for final ascertainment of outcomes.

ART adherence is difficult to accurately assess – patient self-report, pill counts, and MEMS-caps (Medication Event Monitoring System caps are able to record the number of bottle openings and the date and time of each opening) have been used with varying success due to subjectivity and need for participant cooperation (43). Drug levels, treatment or virologic failure, and resistance are more objective measures of adherence long-term. We will use simple, standard measures of adherence (pharmacy refills, and self-reported missed doses at study visits) but rely on the viral suppression measurements as the superior outcome marker of adherence.

h) LABORATORY METHODS

We will conduct maternal HIV viral load testing and infant HIV DNA DBS testing at the branches of the KEMRI/Centers for Disease Control (CDC) located in Kisumu and Nairobi, and CD4 testing at the KEMRI/Centers for Disease Control (CDC) located in Kisumu and Kenyatta National Hospital. Test results will be shared with the clinics and providers to help guide clinical care. Among women with detectable virus, drug resistance will be measured using oligonucleotide ligation assays (OLA) in collaboration with Dr. Lisa Frenkel. OLA assays will be conducted in Dr. Frenkel's laboratory in Seattle Children's Hospital.

i) DATA COLLECTION INSTRUMENTS

Data collection instruments for the RCT will be submitted in a subsequent modification of this protocol. The RCT will not commence until these instruments are reviewed and approved by the UW Human Subjects Department (HSD) and KNH-UoN ethical review committee (ERC). RCT data collection instruments will include forms to record data from:

- Participant surveys: demographics, clinical and sexual history, family planning, disclosure, medication adherence, experience with SMS and technology, intimate partner violence, and depression
- Medical and pharmacy records: delivery information, infant immunizations, maternal health, infant health, medication adherence, lab forms, pharmacy data, maternal mortality, and infant mortality.

j) QUALITY ASSURANCE PROCEDURES

Clinical care: The study will adhere to Government of Kenya guidelines for the care of pregnant/postpartum women and their infants; however, no clinical care will be provided by study staff. Data collected as part of the study will be abstracted from the mother's "Mother & Child Health Booklet" and patient file as well as the MCH clinic's medical records. Counseling and testing for HIV will be performed in accordance with government-approved MCH guidelines. Study participants will receive their HIV medicines in the MCH where PMTCT services are integrated or CCC if PMTCT services are not integrated, enabling reporting of antiretroviral therapy and follow-up in accordance with the national AIDS strategy.

Adherence to protocol: Weekly reporting of enrolment, follow-up, medical complications, laboratory results, and specimen collection will enable us to monitor that the study is running according to approved protocols. Frequent reporting will also enable us to quickly respond to any problems that arise during the study.

Laboratory quality control: The site-specific labs and the KEMRI/CDC laboratory that will process the specimens and conduct most of the laboratory tests are ISO certified, and participates in external quality control verification. For rapid HIV testing, we will use the test kits that have been approved by the Kenya Ministry of Health.

k) TRAINING PROCEDURES

Dr. John Kinuthia will supervise training of clinical personnel in study procedures. This will include research ethics, HIV counseling and testing, infant PCR testing and rapid HIV testing, specimen collection, and completion of surveys.

PHASE 3: POST RCT

a) STUDY DESIGN

IDIs will be conducted by a Kenyan team trained in qualitative research methods and will probe for further elaboration on relevant content from the semi-structured IDI guide. Study investigators experienced in qualitative methods, Dr. John Kinuthia (site-PI) and Dr. Gabrielle O'Malley (co-investigator), have reviewed topic guides for content validity and cultural relevance. We will also conduct surveys among male partners.

b) STUDY POPULATIONS

Female IDIs

After completion of the RCT, we will invite 20 women from 1-way arm and 40 women from 2-way arm to participate in IDIs to understand reasons for success or failure of the intervention in supporting virologic suppression. Within each arm, sampling will be stratified based on VL and SMS engagement (see definitions below and Table 9). Participants will be samples from two study sites (1 in Kisumu and 1 in Nairobi).

Women who exit the RCT will be stratified based on two outcome variables:

a. VL suppression
   i. Participants with suppressed VL will be defined as:
      - Has ≥4 VL results available ≥6mo post-ART initiation
      - ≥2 latest VL results <1000c/ml and ≥6mo post-ART initiation
      - ≥1 earliest VL result ≥1000c/ml and ≥6mo post-ART initiation

   ii. Participants with unsuppressed VL will be defined as:
      - Has ≥2 VL results available ≥ 6mo post-ART initiation (fewer VL results needed so this group may have lower retention also)
      - ≥2 sequential VL results ≥1000c/ml and ≥6mo post-ART initiation and span ≥1 year
      - No ART resistance detected

b. System engagement (among 2-way participants with more than 100 system messages and ≥ 90% of these system messages successfully delivered)
   i. Highly engaged participants will be defined as:
      - Participant's percent weeks active is ≥75th percentile of all participants' percent of weeks active.

   ii. Poorly engaged participants will be defined as:
      - Participant's percent weeks active is ≤25th percentile of all participants' percent weeks active.

Table 9. Female IDIs sampling

Viral load	SMS interaction	site	n	
suppressed	High	Site 1 (Kisumu)	5	10
		Site 2 (Nairobi)	5	
	low	Site 1 (Kisumu)	5	10
		Site 2 (Nairobi)	5	
unsuppressed	high	Site 1 (Kisumu)	5	10
		Site 2 (Nairobi)	5	
	low	Site 1 (Kisumu)	5	10
		Site 2 (Nairobi)	5	
suppressed	NA (one-way)	Site 1 (Kisumu)	5	10
		Site 2 (Nairobi)	5	
unsuppressed	NA (one-way)	Site 1 (Kisumu)	5	10
		Site 2 (Nairobi)	5	
TOTAL				60

These IDIs will be instrumental in understanding whether the intervention did or did not work, why it did or did not work, and possible recommendations for enhancement of the intervention.

Male surveys
We will conduct exit surveys with partners who are referred by intervention arm study participants. Partners will be assessed for eligibility prior to conducting surveys. A total of 80 male partners will be involved (40 from urban, 40 from peri-urban). This approach will be helpful in understanding perceptions of the intervention in terms of benefits to care for mother and child, experiences with SMS, factors that influence the success of the intervention, and enhancement strategies.

Clinic providers IDIs
After the RCT, we will conduct IDIs with 12 MOH healthcare providers (2 per site) to understand their experiences, perceived impacts of SMS intervention on workload, possibilities for scaling up, and share final SMS content with them.

RCT providers IDIs
We will also conduct IDIs with 6 study nurses from the Mobile WAChX study team (1 per site) to understand their experiences of with SMS messaging, barriers and facilitators of use, perceptions of SMS intervention in terms of benefits to care, ability to integrate in long-term care, and recommendations for enhancement of SMS intervention.

c) RECRUITMENT PROCEDURES

Female IDIs: After women complete the RCT, study staff will approach women randomized to either 1-way or 2-way intervention arm with suppressed or unsuppressed VL and low or high engagement with the SMS intervention to describe the purpose of the IDIs and invite interested women to participate. It will be emphasized that participation is completely voluntary. If interested in participation, they will undergo the informed consent process and IDI.

Male surveys: After women complete the RCT, we will sample women randomized to either intervention arm of the RCT and ask them if they would be interested in referring their male partner to participate in a survey about the SMS intervention. Only women who have disclosed their HIV status to their partner and whose partners know about their participation in the RCT will be eligible for study participation. Interested women will be provided a “study clinic referral form” to give their partners (Male Partner survey Post RCT Referral Form). Once partners come for enrollment, they will be given more information on the study. It will be emphasized that participation is completely voluntary. If interested in participation, they will undergo the informed consent process and complete the survey.

Clinic provider IDIs: Health providers working in MCH and CCC will be given information on the RCT and requested to participate in IDIs. Eligible providers are those who are directly involved with care of HIV-infected pregnant women and HIV exposed infants. Those who are willing and able will undergo the informed consent process prior to IDIs.

RCT provider IDIs: Nurses who are recruited by the Mobile WAChX study at all study sites will be given information on the IDIs. Those who are willing to participate and able to provide informed consent will be enrolled.

d) DATA COLLECTION PROCEDURES (clinical and non-clinical, field, data collection instruments)

Both FGDs and IDIs will be performed in a private area. Participants will meet a trained interviewer or moderator who will ask questions and take notes. Consent will be obtained from participants to take notes and audio record the discussion. The interviewer/moderator will describe procedures

and norms for discussion and participation. Participants will be given a chance to ask questions regarding procedures prior to the discussion. Their socio-demographic information will be documented in separate forms. Socio-demographic information that will be captured include: age, marital status, education level, employment, number of children, and partner HIV status as shown in the participant survey portion of each FGD and IDI guide (attached).

Discussions will be guided by the interviewer or moderator using a discussion guide (attached). Prior to FGD, the interviewer will stress the importance of maintaining confidentiality within the group. Participants will receive unique identification numbers and will not be addressed by their real names so as to maintain confidentiality. Topics that generate the most discussion, participant attitudes, non-verbal gestures, and interaction dynamics among group members will be documented by the moderators. Discussions will be conducted in English, Kiswahili, or Luo depending on participant preferences. Thereafter, notes will be compared to audio-recordings to fill in missing information and transcribed to English (if necessary). Transcribed data will be de-identified. Tape-recorded discussions will be destroyed no later than 3 years after conducting the FGD or IDI.

Participants will be provided refreshments and Ksh. 300 to compensate for time and transportation expenses to participate in the study. We will provide this monetary compensation to each participant at the conclusion of each discussion.

e) DATA COLLECTION INSTRUMENTS

Paper copies of data collection tools for IDIs and quantitative ODK questionnaires are submitted with this application for human subjects review.

Table 10: Layout of Phase 3 (Post RCT) procedures, study populations, and eligibility

POST RCT PHASE				
	RCT participants	**Males**	**Clinic providers**	**RCT providers**
Population & maximum sample size	Women N=60 (see Table 9) Stratify by: - RCT arm [1-way/2-way] - Viral suppression [success/failure] - System interaction [high/low] - Clinic [1 Nairobi, 1 Kisumu])	Male partners N=80 (40 urban, 40 peri-urban) By referral through participant in 1-way or 2-way arm	Health providers N=12 (2 per site)	Study nurses N=6 (1 per site)
Study procedures	IDIs	Surveys	IDIs	IDIs
Topic	Experiences and barriers to SMS use, perceived utility and impact, recommendations for improvement. Reasons for high, low or moderate adherence	Evaluate perceptions of women's experiences, perceived impact, concerns/challenge, recommendations for improvement.	Workload, experiences, perceived impact, share final SMS content, possibilities for scale	Workload, improvements, possibilities for scale

	and low or medium responsiveness Impact of SMS on resulting adherence			
Recruitment	RCT participant	Through female RCT participant	MCH, CCC	Study staff
Eligibility	• Randomized to one of the intervention arms (one way or two way SMS)	• Has partner randomized to one of the intervention arms in RCT • Partner disclosed her HIV status to male partner • Partner aware of RCT participation • Willing to provide an informed consent • Age ≥18	• Nurses, Clinical officers, Mother to mother, Peer counselors • Directly involved with care of HIV-infected pregnant women and HIV exposed infants • Willing to provide informed consent	• Mobile WAChX study nurse at any point in the study • Willing to provide informed consent

11) STUDY MATERIALS:

Equipment: The grant award includes support to purchase one -80C freezer to store study specimens, SMS platform messaging delivery and receipt, 4 tablets, field office supplies (stationary, paper, toner), 4 desktop computers, clinic supplies to collect and store biological samples.

Personnel: The grant award includes support for UW investigators, clinic personnel, the data team, and a study coordinator. Study personnel working in Kenya will be hired through KNH according to standard procedures.

Costs data

We will assess the cost of all services and equipment necessary to implement each of the three arms (direct medical costs). Using WHO guidelines and its ingredients approach (45, 46) direct medical costs will quantify the resources and associated unit costs to deliver each intervention, organized in standard expenditure categories: personnel (salaries), supplies including drugs and medications, equipment (e.g. computer programming), services (e.g. airtime, media, costs related to the mHealth such as cellular phones, wireless network), space and overhead, community awareness and mobilization. A particular emphasis will be put on the measurement of the costs incurred by treatment failure and drug resistance, as well as on the costs for the different types of personnel employed (e.g. nurses) and the time demanded from them in each intervention (unidirectional SMS vs. bidirectional SMS messaging). In addition, direct non-medical costs quantifying transportation costs, food and housing expenses, and user fees; and indirect costs quantifying the time loss for patients to seek care and associated lost wages, due to long waiting times will be assessed in participant surveys.

12) ETHICAL CONSIDERATIONS

Data Ownership

The proposed project is a collaborative effort between investigators at the UW and KNH. The aforementioned institutions will jointly share ownership of the data. Study investigators at the UW and KNH will have full access to the data. Authorship on publications, conference presentations, abstracts and other materials generated from this study will reflect contribution to design, execution and analysis of the study.

Data Release/Sharing Policy

All data collected as part of this proposed research project will be made available without cost after registration to access or download files on a study related website (URL to be determined) and agreement to the data sharing agreement. The data sharing agreement will ensure commitments to:

1. Using the data only for research purposes and without attempting to identify study participants (if applicable);
2. Securing the data using appropriate computer technology;
3. Destroying or returning the data after analyses are completed;
4. Restrictions on redistribution of the data to third parties; and
5. Proper acknowledgement of the data resource.

13) STUDY LIMITATIONS AND HOW TO MINIMIZE THEM:

The study evaluates several concepts, first whether SMS decreases maternal virologic failure, enhances infant HIV prevention, decreases resistance and preserves regimens. The study is powered for maternal outcomes but may have power to detect effects on infant HIV-free survival and a variety of secondary outcomes. Data from maternal viral load effects could inform future models of down-stream impacts of the intervention on infant and sexual HIV transmission. We intentionally designed the study to have long follow-up time (rather than larger cohort with short follow-up) because long-term PMTCT-ART outcomes are the most relevant for policy/programs. Second, the study will evaluate whether dialogue has a discernable advantage over simple unidirectional messaging. This is a novel comparison, not previously addressed in mHealth studies with important implications both for HIV and other chronic medical conditions. Fidelity and generalizability of dialogue interventions are challenging. We have proposed SOP-driven dialogue and implementation and evaluation in two sites to address these issues, but it will not be possible to completely standardize bidirectional interventions. Finally, defining programmatic cost-savings or effectiveness is based on specific time/costs of the sites. We believe that these sites reflect other national and regional settings.

14) TIMELINE/ TIME FRAME:

	2014	2015	2015	2016	2017	2018	2019	2020
Checklist Item	**Oct- Dec**	**Jan- Jun**	**Jul-Dec**	**Jan-Dec**	**Jan-Dec**	**Jan-Dec**	**Jan- Dec**	**Jan-Dec**
Study protocol developed	X							
Develop FGD guides	X							
Consent forms developed	X							
Kiswahili translated consent	X							
IRB/ERC applications	X							
Study specific SOP/CRF training		X						
Trainings-HSR,mHealth, data mx		X						
Database development		X						
mHealth system		X						
CRFs	X	X						
SOPs	X	X						
FGD		X					X	
RCT		X	X	X	X	X	X	

Data collection		**X**	**X**	**X**	**X**	**X**	**X**	
Data analysis							**X**	
Manuscript writing							**X**	**X**
Fiscal close-out								**X**
Dissemination of results								**X**

15) HUMAN SUBJECTS

Ethical Approval

We will obtain ethical approval from the University of Washington (UW) Human Subjects Division and the Kenyatta National Hospital-University of Nairobi Ethics and Research committee .

Collaborating sites

The study will be conducted in collaboration with the UW, KNH, KEMRI, and CDC. The study will be reviewed by the KNH ERC and UW IRB and will not be started before approvals are obtained from all two organizational review boards. For this specific study, University of Washington investigators will not be directly involved in fieldwork, data collection, or study recruitment or consenting processes. Data analysis performed by investigators, co-investigators and personnel will be performed using only de-identified data.

LIST OF ABBREVIATIONS

ANC	Antenatal Care
APHIA-plus	AIDS, Population and Health Integrated Assistance
ART	Antiretroviral Therapy
ARVs	Antiretroviral drugs
CCC	Comprehensive Care Clinic
CDC	Centers for Disease Control and Prevention
CTX	Cotrimoxazole
DNA	Deoxyribonucleic Acid
ERC	Ethics Review Committee
GoK	Government of Kenya
HAART	Highly active antiretroviral therapy
HEI	HIV-exposed infant
HIV	Human Immunodeficiency Virus
HAZ	Height-for-age Z-score
ICAP	International Center for AIDS Care and Treatment Programs
IRB	Institutional Review Board
KEMRI	Kenya Medical Research Institute
KNH	Kenyatta National Hospital
M2M	Mothers-to-Mothers
MCH	Maternal and Child Health
MOH	Ministry of Health
MTCT	Mother-to-Child Transmission
NASCOP	National AIDS and STI Control Program
ODK	Open Data Kit
OI	Opportunistic Infections
OLA	Oligonucleotide Ligation Assays
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother-to-Child Transmission of HIV
PNC	Postnatal Clinic
RCT	Randomized Controlled Trial
SMS	Short Messaging System
UON	University of Nairobi
UW	University of Washington
WHO	World Health Organization

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