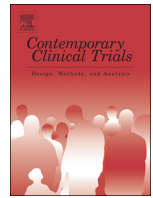




Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Evaluation of mHealth strategies to optimize adherence and efficacy of Option B+ prevention of mother-to-child HIV transmission: Rationale, design and methods of a 3-armed randomized controlled trial

Alison L. Drake^{a,*}, Jennifer A. Unger^b, Keshet Ronen^c, Daniel Matemo^d, Trevor Perrier^e, Brian DeRenzi^f, Barbra A. Richardson^g, John Kinuthia^d, Grace John-Stewart^h

^a Department of Global Health, University of Washington, Box 359909, Seattle, WA 98195-7236, USA

^b Departments of Global Health and Obstetrics and Gynecology, University of Washington, Box 359909, Seattle, WA 98195-7236, USA

^c Departments of Global Health and Epidemiology, University of Washington, Box 359909, Seattle, WA 98195-7236, USA

^d Department of Research and Programs, Kenyatta National Hospital, PO Box 20723-00202, Nairobi, Kenya

^e Department of Computer Science and Engineering, University of Washington, Box 352350, Seattle, WA 98195-7236, USA

^f Department of Computer Science, University of Cape Town, Room 306, Computer Science Building, Cape Town, South Africa

^g Department of Biostatistics, University of Washington, Box 359909, Seattle, WA 98195-7236, USA

^h Departments of Global Health, Medicine, Epidemiology, and Pediatrics, University of Washington, Box 359909, Seattle, WA 98195-7236, USA

ARTICLE INFO

Article history:

Received 18 October 2016

Received in revised form 1 March 2017

Accepted 13 March 2017

Available online 14 March 2017

Keywords:

mHealth

Antiretroviral therapy

Adherence

Pregnancy

Prevention of mother-to-child HIV transmission

SMS

ABSTRACT

Background: Lifelong antiretroviral therapy (ART) (Option B+) is recommended for all HIV-infected pregnant/postpartum women, but high adherence is required to maximize HIV prevention potential and maintain maternal health. Mobile health (mHealth) interventions may provide treatment adherence support for women during, and beyond, the pregnancy and postpartum periods.

Methods and design: We are conducting an unblinded, triple-arm randomized clinical trial (Mobile WACH X) of one-way short message service (SMS) vs. two-way SMS vs. control (no SMS) to improve maternal ART adherence and retention in care by 2 years postpartum. We will enroll 825 women from Nairobi and Western Kenya. Women in the intervention arms receive weekly, semi-automated motivational and educational SMS and visit reminders via an interactive, human-computer hybrid communication system. Participants in the two-way SMS arm are also asked to respond to a question related to the message. SMS are based in behavioral theory, are tailored to participant characteristics through SMS tracks, and are timed along the pregnancy/postpartum continuum. After enrollment, follow-up visits are scheduled at 6 weeks; 6, 12, 18, and 24 months postpartum. The primary outcomes, virological failure (HIV viral load ≥ 1000 copies/mL), maternal retention in care, and infant HIV infection or death, will be compared in an intent to treat analysis. We will also measure ART adherence and drug resistance.

Discussion: Personalized and tailored SMS to support HIV-infected women during and after pregnancy may be an effective strategy to motivate women to adhere to ART and remain in care and improve maternal and infant outcomes.

© 2017 Elsevier Inc. All rights reserved.

Abbreviations: ANC, antenatal care; ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; eMTCT, elimination of mother-to-child HIV transmission; FGD, focus group discussion; IDI, in-depth interviews; KEMRI, Kenya Medical Research Institute; mHealth, mobile health; MCH, maternal child health; MTCT, mother-to-child HIV transmission; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside/tide reverse transcriptase inhibitors; ODK, Open Data Kit; OLA, oligonucleotide ligation assay; PCR, polymerase chain reaction; PY, person-years; PMTCT, prevention of mother-to-child HIV transmission; RCT, randomized clinical trial; SMS, short message service; WHO, World Health Organization; HTTP, Hypertext Transfer Protocol.

* Corresponding author.

E-mail addresses: adrake2@uw.edu (A.L. Drake), junger@uw.edu (J.A. Unger), keshet@uw.edu (K. Ronen), daniel.matemo@gmail.com (D. Matemo), tperrier@cs.washington.edu (T. Perrier), bderenzi@cs.uct.ac.za (B. DeRenzi), barbrar@uw.edu (B.A. Richardson), kinuthia@uw.edu (J. Kinuthia), gjohn@uw.edu (G. John-Stewart).

1. Introduction

In 2015, 110,000 children became infected with HIV in 21 of the highest burden countries in sub-Saharan Africa, primarily through mother-to-child HIV transmission (MTCT) [1]. This estimate represents a 60% reduction in MTCT over a six-year period, due to provision of antiretroviral regimens to women and infants in prevention of mother-to-child HIV transmission (PMTCT) programs [2].

Lifelong antiretroviral therapy (ART) for all HIV-infected pregnant women, known as PMTCT Option B+, was recommended in 2013. This efficacious PMTCT regimen requires consistent retention and maternal adherence to treatment. However, retention in adult ART programs wanes over time, with an estimated 30% of patients being lost

to follow-up in programs after two years [3]. Within PMTCT programs, loss to follow-up varies, ranging from 19 to 85% [4,5]. Implementation of Option B+ in PMTCT programs has resulted in higher ART coverage and lower MTCT rates, but barriers to retention and adherence persist [6–9]. ART adherence may decline following delivery and throughout the first year postpartum [8]. Mothers may lose motivation to continue ART for their own health after they stop breastfeeding [10,11]. Poor ART adherence leads to virologic failure and potential development of ART resistance, limiting effectiveness of ART regimens.

In general, adherence to ART and retention in care are affected by sociobehavioral, clinical, and health systems factors, including self-efficacy, stigma, partner and family support, side effects, and patient-provider interactions [11–14]. Treatment support to encourage adherence and retention is offered at clinic visits; however, clients may face challenges at home and barriers to clinic attendance that could be addressed by tailored treatment support via phone messaging services.

Mobile health (mHealth) interventions provide an attractive approach to enhance HIV treatment support for Option B+ PMTCT. In a meta-analysis of 16 randomized clinical trials (RCTs) of short message service (SMS) interventions, including several studies on HIV in sub-Saharan Africa, SMS interventions improved medication adherence for chronic conditions > 2-fold [15]. SMS was found to be effective for increasing antenatal and postnatal attendance among HIV-infected women and improving early initiation and exclusive breastfeeding [16]. However, the effect of SMS on maternal or infant outcomes, including maternal ART adherence to Option B+ has not been assessed in RCTs. In addition, few mHealth interventions in resource-limited settings target or tailor SMS content, which may limit their potential [17].

We adapted an interactive mHealth human-computer hybrid communication system initially designed for maternal child health (Mobile Solutions for Women's and Children's Health, Mobile WaCh) [18], to address PMTCT-ART related outcomes in Mobile WACH X. We designed a 3-armed RCT to determine the impact of one-way SMS vs. two-way SMS vs. control (no SMS) on maternal ART adherence, retention in care, and infant HIV infection or death during 2-year postpartum follow-up.

2. Material and methods

2.1. Study design and population

The RCT is conducted in 3 sites in Kenya, 2 rural sites in the Nyanza region (Ahero County Hospital and Bondo sub-County Hospital), and 1 urban site in Nairobi (Mathare North Health Center). Women are eligible to participate if they are ≥14 years old, attending antenatal care (ANC), HIV-infected, ≤36 weeks gestation, have daily access to a mobile phone (own or shared) with a Safaricom SIM card, are willing to receive SMS, plan to reside in the area for two years postpartum, plan to receive both maternal child health (MCH) and HIV care at the facility they were recruited from, and are not enrolled in any other studies. Women who are illiterate but are comfortable with another person reading them the SMS are eligible for the study. In April 2016, eligibility criteria were expanded to include women >36 weeks gestation.

Study procedures and data collection instruments were approved by ethical review committees at the Kenyatta National Hospital/University of Nairobi and the University of Washington. Participants provide written informed consent prior to enrollment in the study.

2.2. Randomization

The RCT involves 825 participants randomized to one-way SMS, two-way SMS, or control (no SMS) using 1:1:1 allocation. Randomization is stratified by site (no more than 399 women will be randomized from any site). A randomization list was generated using variable block sizes in Stata 12.1 ralloc.ado v.3.5.2. Allocation codes were placed in sequentially numbered sealed, opaque envelopes by site which are

sequentially distributed to and opened by participants. Study investigators are blinded to block number, size, and sequence.

2.3. Intervention

Women randomized to one-way SMS or two-way SMS receive weekly, automated motivational and educational messaging as well as clinic visit reminders. SMS for participants in the two-way SMS arm also include a question related to the message topic that solicits, but does not require, a response. In addition, women in the two-way arm can communicate with the study nurse via SMS at any time.

Formative research was conducted to develop SMS messages for the Mobile WACH X RCT. MCH-related SMS were adapted from a prior trial (Mobile WACH) which evaluated one-way SMS vs. two-way SMS vs. control as a strategy to improve MCH outcomes in Kenya, and HIV-related SMS were newly developed and tested [18]. SMS message content was adapted through a series of focus group discussions (FGDs) with HIV-infected pregnant and postpartum women, key informant in-depth interviews (IDIs) with health providers, and IDIs with male partners of HIV-infected women. (Fig. 1) FGDs were conducted until saturation was achieved by site (urban and rural). Results from these studies were used to determine acceptability and comprehension of pre-developed SMS themes and content, elicit suggestions for additional message themes and/or phrasing, understand and address concerns about SMS, and refine SMS. Results from qualitative studies are summarized elsewhere (manuscript under review).

SMS are managed through a semi-automated, open source human-computer hybrid communication SMS system developed by investigators at the University of Washington (Fig. 2). The platform incorporates Reinforcement Theory [19], in this case positive reinforcement theory, to motivate completion of tasks by study staff, such as message responses, patient tracking updates, and coding of SMS for streamlined monitoring and evaluation. The system is a custom web application hosted on a password protected virtual private server written using the Django web-framework and Angular.js. SMS are sent to, and received by, participants free of charge on a short code through a Hypertext Transfer Protocol (HTTP) to SMS gateway maintained by a Kenyan premium rate service provider (Fig. 3). Study staff access the system through a desktop web browser and are able to respond to incoming SMS messages, monitor upcoming and missed visits, document phone calls and translate messages for uniformity in understanding message content. The system also includes an interface that provides a summary of participant details (maternal age, expected or actual delivery date, pregnancy or postpartum status, ART status, family planning method, and randomization arm) for study staff to have essential information about women when they are using the system. Pre-programmed SMS are automatically sent to women randomized to one-way and two-way arms weekly at the participant's preferred time of day, day of week, and language (English, Kiswahili, or Dholuo).

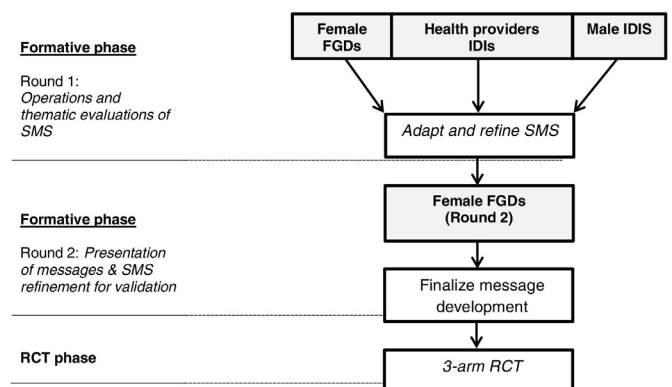


Fig. 1. Formative research for SMS adaptation and refinement.

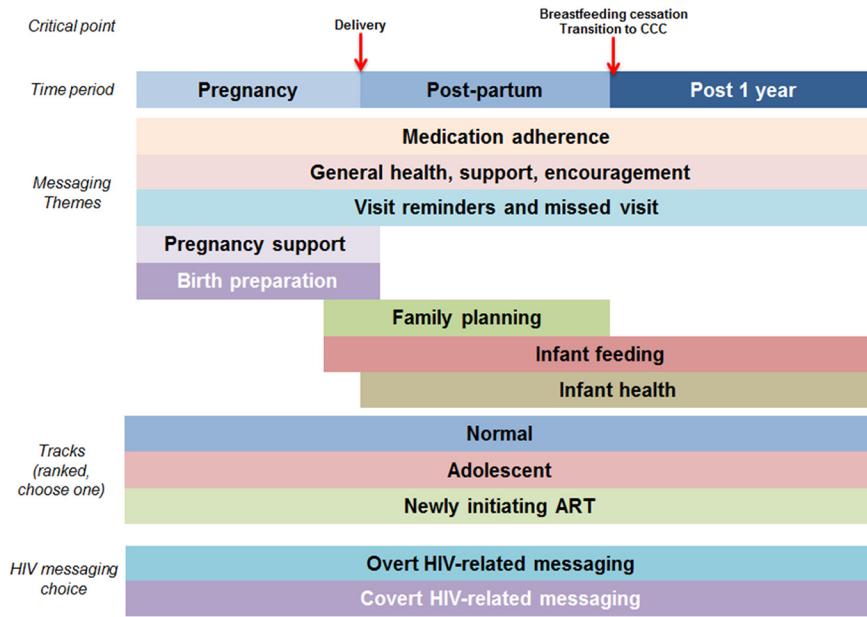


Fig. 2. SMS message themes and tracks.

SMS content addresses a range of topics, including ART adherence, pregnancy support and education, birth preparedness and delivery, infant feeding, infant health, family planning, and appointment reminders (Fig. 4). SMS are based on the Health Belief Model and Social Cognitive Theory [20,21], in order to provide tailored and actionable education, support, counseling, and reminder messages designed to reinforce health behaviors such as clinic attendance and ART adherence. SMS topics are scheduled according to antenatal/postnatal timing and ART experience. Visit reminder SMS are sent 3 days before the scheduled appointment date and congratulatory SMS are sent when visits are attended. Additional reminders are sent 3 and 6 days after a missed visit.

RCT participants are asked at the time of consent whether they would like to receive SMS that contain HIV-related terms (such as ‘medications’, ‘infection’) and topics (side-effects, PMTCT, infant prophylaxis, infant testing). In order to protect patient confidentiality and prevent involuntary disclosure, women are only eligible to receive HIV-related content if they have disclosed their status to anyone who has access to their phone or if no one has access to their phone. Women can elect one of the following options: 1) not receive any overt HIV-related content, 2) receive overt HIV-related SMS only in response to a question asked by the participant to the study nurse, or 3) receive overt HIV-related SMS as part of regular weekly SMS sent to participants and in response to a question asked by the participant to the study nurse. Preferences on HIV-related content are asked of all women prior to randomization.

Examples of SMS developed through iterative formative research are shown in Table 1. For each SMS, we developed up to 16 versions, customized based on the intervention arm (one-way or two-way), preference for HIV-related messaging (overt or covert), and participant ‘track’ based on participant characteristics (previously on ART, newly initiating ART, or adolescent track). Fig. 4 summarizes the message content and tracks. One-way and two-way SMS are the same with the exception of the addition of a question that prompts women to reply in the two-way SMS arm. Participants are entered into one of the messaging tracks at enrollment. Additionally, a separate track was developed for participants who experience a fetal or infant loss after enrollment and provides women with similar SMS that do not mention the baby. If study staff are informed of the loss, they call the participant to offer condolences and ask if she wants to continue in the study. Women who opt to continue study participation in the intervention arms are also asked if they want to continue receiving SMS, and if so, are switched to the fetal/infant loss track. While the SMS database continues to expand as the study progresses, to date, we have 676 unique English versions of SMS that are sent to women between 16 weeks gestation and 45 weeks postpartum: 236 antenatal SMS; 400 postpartum SMS; and 40 visit reminder, condolence, and system administrative SMS. The full message database is available on request from the authors and will be made publicly available by the completion of the study.

Women can stop receiving SMS at any time by sending the message ‘STOP’ to the study short code; they can elect to either stop all SMS or stop education and counseling SMS but continue with visit reminders.

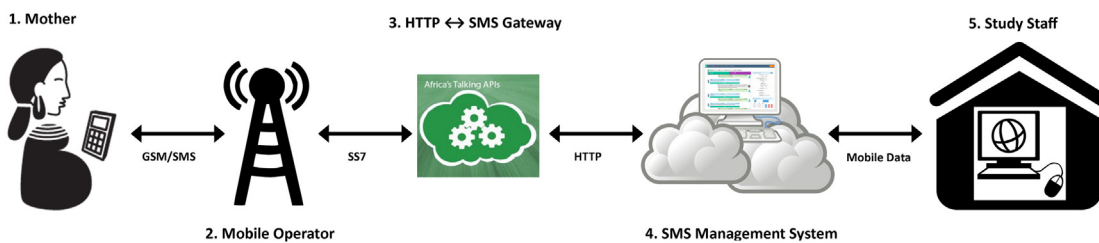


Fig. 3. SMS system architecture. Women (1) receive SMS messages on Safaricom using the standard GSM/SMS protocol. The Kenyan premium service provider (3) receives SMS messages over SS7 from Safaricom (2) and forwards them to the SMS management system on a virtual private server (4). Study staff can access the SMS management system to reply to SMS from women via a laptop and mobile data (5).

The screenshot shows the 'Mama Baby' SMS system interface. At the top, there is a navigation bar with icons for Home, Messages, Visits, Calls, Translations, and Participants. Below this, the study name 'Mama Baby' is displayed along with Study ID, ANC #, CCC #, and 'TWO-WAY'. A secondary bar contains 'Send Msg' and 'Call Log 2' buttons. The main content area shows a message thread: a system message from Valarie from Bondo about breastfeeding, a reply from Mama Baby, and a reply from a Nurse. On the right, there is a 'Participant Details: Mama Baby' table and a 'Clinic Visits and History' section.

Participant Details: Mama Baby	
Phone number	+254700000000
Status	Post-Partum
Estimated Delivery Date	2016-??-??
Delivery Date	2016-??-??
Age	38
Send Day	Friday
Send Time	Evening (8 PM)
SMS Track	4 - Normal
ART Initiation	2016-??-??
Previous pregnancies	3
HIV Disclosure	Yes
HIV Messaging	HIV Content Allowed

Clinic Visits and History		
Date	Type	When

Fig. 4. SMS system screenshot.

2.4. Study procedures

Women are enrolled during pregnancy and have follow-up visits scheduled at 6 weeks; 6, 12, 18, and 24 months postpartum. At each study visit, women are administered a standardized survey on a tablet using Open Data Kit (ODK). A summary of survey data at each visit, and instruments used for collection are described in Table 2. All clinical procedures, including MCH and HIV related care, are provided by clinic staff; no clinical care is provided by the study. Between study visits, study staff abstract patient records to inform personalized, dynamic messaging. Study staff record appointments, deliveries, clinic visits, medication refills, infant immunizations, or any clinic contact with study participants.

Maternal blood samples are collected at enrollment for HIV viral load, and for CD4 count at enrollment, 12 and 24 months postpartum. HIV viral load at enrollment is conducted by the study; follow-up assays are performed as part of the standard of care every 6 months and results are abstracted from maternal records. All maternal HIV viral loads conducted by the study and the program are performed at the Kenya Medical Research Institute (KEMRI)/Centers for Disease Control and Prevention (CDC) in Kisumu or Nairobi, Kenya using the Roche COBAS® TaqMan® Analyser or COBAS® TaqMan® Version 2.0 (CAP/CTM v2.0) platform. In the event that HIV viral load cannot be performed for any reason as part of the standard of care, viral loads are performed by the study. Infant dried blood spots are collected at each postpartum study visit. Infant HIV DNA polymerase chain reaction [PCR] testing is conducted as part of PMTCT programs at 6 weeks, 6 months, and 12 months. Programmatic infant HIV test results are abstracted from clinic records. The study will also test infants at 24 months using 4th generation HIV tests.

Since retention in care is a primary trial outcome, retention efforts and contact with study participants are minimized in order to avoid contamination of the intervention. Phone numbers of participant contacts and locator information following a home visit are collected at enrollment, to re-establish contact at 24 months postpartum for participants who are lost to follow-up. In addition, phone calls are made to all participants at 1 month following their expected delivery date to determine delivery date and align postpartum messages. Phone calls are also

made at 12 months to all women, and at 24 months if women miss the exit study visit. In addition, for severe adverse events the study team calls participants to learn more about the events and evaluate intervention relatedness.

3. Outcomes and statistical analyses

The primary study outcomes are maternal virologic failure, maternal retention in care, and infant HIV infection or death; secondary outcomes include maternal ART adherence and drug resistance (Table 3). Clinical, laboratory, and behavioral outcomes are captured via participant surveys and data abstracted from MCH booklets, HIV clinic records and registers for PMTCT, labor and delivery, pharmacy, and peer counseling (Mothers2Mothers). Women initiating ART who have ≥ 1000 copies/mL 6 months after ART initiation will be classified as having virologic failure. Retention in care will be evaluated at 12 and 24 months postpartum and defined as the proportion of clinic visits attended within 2 weeks of the scheduled date. ART adherence will be calculated based on data abstracted from pharmacy records (proportion of days covered for each refill interval) and self-reported surveys (proportion of doses missed in the last 30 days at each study visit). Women are classified as having antiretroviral drug resistance if resistance mutations are detected from women with HIV RNA levels exceeding 200 copies/mL using an oligonucleotide ligation assay (OLA) capable of detecting codon mutations conferring resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) (K103N, Y181C, and G190A) or nucleoside/tide reverse transcriptase inhibitors (NRTI) tenofovir (K65R) lamivudine/emtricitabine (M184V). These OLA probes are optimized for HIV subtypes A, D, and C common in Kenya [22].

Intention-to-treat analyses will be used to conduct the primary statistical analyses; we will compare each intervention arm (one-way and two-way SMS) individually to the control arm. In addition, per-protocol analyses will be conducted which exclude women who request to stop receiving SMS and those who require additional retention efforts (phone call or home tracing) at 24 months postpartum and to compare a composite intervention group (one- or two-way SMS vs. control). Chi-square and Kruskal-Wallis tests will be used to compare baseline characteristics in each arm and determine whether randomization

Table 1
SMS topics and examples included in Mobile WACH X.

Topic	Example SMS
Message preamble ^a	<Name>, it is <nurse> from <x> clinic
Medication adherence	Your health is very important. Take time each day for your health. If you are having challenges, let us know. <i>Are you having any challenges this week?</i>
HIV medication (overt) ^b	Your health is very important. Make sure to take your medication every day and come in for more when you need them. If you are having challenges let us know. <i>Are you having any challenges with your medications? When are you due to come in for more?</i>
General encouragement ^c	If you are having any health concerns we are available to help
Visit reminder	It's time for your clinic visit in <days> days on <date>. If you have any questions, ask the nurse. <i>Are you planning to come in to clinic on this date?</i>
Missed visit	We missed you in clinic today. You are due for your visit. Please come in. <i>Are you having trouble getting to clinic? When will you come in?</i>
Attended visit	Great job coming in for clinic. You are taking good care of both you and your growing baby. <i>Are you feeling well? Do you have any concerns? Breastfeeding a baby right after birth helps the milk come. The first yellow sticky milk has many vitamins & cleans out the stomach. Milk has all the water the baby needs, avoid other liquids. Are you planning to breastfeed?</i>
Infant feeding	Your baby will receive important vaccines at the next visit. Please bring your book and ask your nurse to check you receive everything. <i>Do you have any questions?</i>
Infant immunization reminder	The IUCD or coil is a small device for family planning. Easy to put in, safe and very effective for years but can be removed at any time! Ask about the coil at your family planning visit. <i>Do you know anyone who has the coil?</i>
Family planning	Regular, strong contractions are a sign of labour. If you feel strong tightening of your belly, leaking of fluid or any bleeding go to the clinic. Don't wait. <i>Do you feel any contractions?</i>
Birth preparedness counseling	

Italics indicate additional SMS content included in messages sent to women in the two-way arm.

^a All SMS initiated by the Mobile WACH X system start with this introduction, followed by the topic specific message.

^b SMS content included with other messages, but not sent on its own.

^c HIV-related SMS are only sent to women who elect and provide specific consent to receive these types of messages.

was balanced. Cox proportional hazards regression will be used to compare virologic failure 6 months after enrollment (time starting 6 months post-enrollment), infant HIV infection or death, and incidence of drug resistance. Chi-square tests will also be used to compare proportions of women in each arm who develop resistance by 24 months postpartum. Logistic regression will be used to compare differences in the

proportion of women lost to follow-up in each arm and ANOVA will be used to compare completeness of visit attendance at 12 and 24 months postpartum. ANOVA will also be used to compare ART adherence at 6, 12, and 24 months postpartum.

We will conduct activity-based costing to assess direct medical costs associated with the intervention using World Health Organization (WHO) guidelines, including personnel, supplies, services, space, and community awareness and mobilization. Treatment costs incurred due to treatment failure and drug resistance, and time for study staff to reply to one-way and two-way SMS will also be measured. Direct non-medical costs (transportation costs, user fees) and indirect costs quantifying the time loss and lost wages for patients to seek care will be assessed in surveys. Costs will be incorporated into a cost-effectiveness model that will measure incremental costs and cost-effectiveness of one-way SMS and two-way SMS vs. control, and between intervention arms. Cost-effectiveness will be performed from both the provider and societal perspectives.

4. Sample size calculation

With 825 women randomized in a 1:1:1 allocation ratio (275 women per arm); assuming alpha = 5%, power = 80%, 2-sided testing, and allowing for 10% attrition; we have sufficient power to detect a hazard ratio (HR; treatment vs. control) of <0.65 for virologic failure assuming an incidence rate of 25 per 100 person-years (PY) in the control arm, a HR of <0.65 for loss to follow-up, assuming an incidence rate of 25 per 100 person-years (PY) in the control arm; and a HR of <0.55 for drug resistance, assuming an incidence rate of 15 per 100 PY in the control arm. We also have sufficient power to detect a HR of >2.0 for infant HIV infection or death, assuming an incidence rate of 10 per 100 PY in the control arm. Thus, the total cohort sample is 825 women.

5. Discussion and conclusions

In the Mobile WACH X trial, we will evaluate both one-way and two-way SMS communication as strategies to improve maternal ART adherence and retention in HIV care and treatment programs. Investment in approaches that help women overcome barriers to ART adherence can reduce MTCT, improve maternal health, reduce risk of heterosexual transmission, and prepare women to have healthy subsequent pregnancies.

With the rapid expansion of mobile phone access, SMS messaging has enormous potential to expand the reach of healthcare providers to improve HIV-related outcomes in resource-limited settings. There is evidence that two-way messaging improves clinic attendance and medication adherence, including HIV medications; [15,17], but trials evaluating SMS potential to improve long-term maternal ART adherence in PMTCT settings, or combine both MCH- and HIV-related message content, have not been conducted. Most studies evaluating SMS interventions for HIV-related outcomes predominantly focus on

Table 2
Survey topics, timing of administration, and instruments used.

Survey topic	Timing	Instrument for assessment
Demographics	Enrollment	
Antiretroviral therapy use, adherence, and knowledge	All study visits	15 items from the LifeWindows ART adherence questionnaire [38]
Disclosure	All study visits	
Social support	All study visits	Medical Outcomes Study survey [39]
Stigma	All study visits	4-item instrument adapted from the stigma scale for chronic illnesses (SSCI) [40]
Maternal depression	All study visits	Patient Health Questionnaire 9 (PHQ-9) [41]
Intimate partner violence	All study visits	Abuse Assessment Screen [42]
Maternal health	All study visits	
Family planning	All study visits	
Food security	All study visits	
Use of technology	Enrollment and 24 months postpartum	Household Food Insecurity Access Scale (HFIAS) [43]
Infant feeding practices	Enrollment and 24 months postpartum	

Table 3
Primary and secondary outcomes.

	Indicator	Source
<i>Primary outcomes</i>		
Maternal virologic failure	HIV RNA \geq 1000 copies/mL	Maternal blood at 6 week; 6, 12, 18, 24 months postpartum
Retention	Seen within 2 weeks of scheduled visits	Record abstraction for scheduled clinic visits throughout study. Evaluated at 12 and 24 months
Loss to follow-up	Not seen in clinical care for \geq 6 months	Record abstraction for scheduled clinic visits throughout study
Infant HIV infection or death	HIV DNA and antibody results, and mortality	Record abstraction week 6. Infant specimens 6, 12, 18, 24 months; verbal autopsy
<i>Secondary outcomes</i>		
Drug adherence	<ul style="list-style-type: none"> • Pharmacy: % days covered since last refill^a • Self-report: % doses taken in last 30 days 	Pharmacy: record abstraction throughout study Self-report: questionnaire at study visits 6 wk., 6, 12, 18, 24 months
Maternal drug resistance	OLA	Resistance assay in mothers with HIV RNA exceeding 200 copies/mL

^a Pharmacy data will be considered as higher quality.

medication and treatment reminders, which may underutilize the potential of this communication modality. Messaging that incorporates education and patient support to continue ART, while simultaneously reducing healthcare worker burden, may be an effective way to harness the power of mHealth technology and move beyond appointment and medication reminders.

Few mHealth intervention studies use viral load data to assess adherence; [24] most have primarily relied on self-reported adherence, which overestimates adherence [25]. We will use viral load and resistance testing, in addition to self-report, to better characterize adherence. We will also capture barriers to adherence reported during study visits, and collect “real-time” qualitative data from women in the two-way arm who relay adherence related information via SMS responses. A recent meta-analysis found that two-way SMS provided a 23% increase in adherence to medications, while one-way SMS provided no benefit [23]; however, none of the studies included in this analysis directly evaluated or compared two-way vs. one-way SMS within the same study, population, or setting. One-way SMS that incorporate education and counseling, and support maternal and child health in addition to medication adherence, could be effective in PMTCT settings. If one-way SMS are shown to be effective they may be easier to implement or incorporate into existing programs than two-way SMS. Alternatively, two-way SMS could enhance patient engagement through an interactive exchange with providers, but is more expensive than one-way SMS. In Mobile WACH X, we will evaluate potential public health benefits and cost of each intervention vs. control, and assess any incremental benefit of two-way vs. one-way SMS. Cost-effectiveness modeling will provide further insights to determine the economic impact of implementing each approach.

The content of Mobile WACH X provides personalized, tailored, and dynamic SMS messages that are informed by behavioral theory. These qualities have previously been reported to be desired components of SMS, and may enhance effectiveness of mHealth interventions [26–30]. SMS in Mobile WACH X include the participant’s preferred name or nickname and provider name, and participants receive visit reminders based on their individual appointment schedule. SMS content follows a topic schedule designed to encourage ART adherence while recognizing concerns specific to salient events in pregnancy and the postpartum period, such as delivery, infant prophylaxis, and weaning. Additionally, participants are placed in a messaging “track”, which deliver content tailored to the participant’s age group (adolescent vs. adult), and/or key clinical characteristics (newly initiating ART or fetal/infant loss). Infant mortality remains high among infants born to HIV-infected mothers in Africa, [31–33] and women may lack motivation to continue ART or seek health care following a pregnancy loss. Mobile WACH X’s infant/fetal loss track provides these women with support to maintain their own health during this critical time period. Together, the Mobile WACH X tracks allow for SMS customization, which enhances personalization and may increase effectiveness compared to a universal one-size-fits-all approach.

Our study is subject to some limitations. While literacy is not required for women to participate, illiterate women need to feel

comfortable with another person reading SMS to them. Many women share their phone with a partner or family member, and only women who have daily access to a mobile phone, and feel comfortable with individuals who share their phone reading study-related SMS, are eligible for the study. In addition, women who receive MCH and HIV care at multiple facilities are also ineligible. While Safaricom is the most commonly used mobile phone carrier in Kenya (68% of all mobile phone subscribers) [34], women who do not have a Safaricom SIM cannot be enrolled in the Mobile WACH X system, and are also excluded from the study. Thus, study results may not be generalizable to women who are not comfortable sharing SMS, receive care in multiple facilities, or use other mobile phone carriers. In addition, we will not adjust for multiple comparisons in our analysis which may increase the Type I error rate.

The Mobile WACH X study is unique in its personalized and tailored approach to provide HIV-infected women with support during and after pregnancy, and ability to determine the optimal level of participant interaction by directly evaluating potential health and economic benefits of one-way vs. two-way SMS dialogue. The study was intentionally designed with a long follow-up time, beyond the recommend 12 month period HIV-infected women are advised to continue breastfeeding [35], to assess intervention impact beyond PMTCT and long-term durability. mHealth has been identified as a priority area for research in efforts to eliminate mother-to-child HIV transmission (eMCT) [36], but data are lacking on the effectiveness of mHealth for HIV-related maternal and infant outcomes. mHealth interventions for PMTCT may be particularly effective if they are initiated during pregnancy, motivating women to make positive behavior changes to benefit the health of their baby and their own health [37]. Results from our study will contribute important data on the utility of SMS for PMTCT and HIV and could help inform strategic programmatic investments to improve maternal and child health outcomes.

6. Trial status

Recruitment and enrollment for the RCT began on 23 November 2015. We anticipate completing enrollment by April 2017 and all follow-up activities by January 2020.

Acknowledgements

We would like to acknowledge the significant contributions from study participants and the Mobile WACH X team members. We would also like to acknowledge support from the University of Washington’s Global Center for Integrated Health of Women, Adolescents and Children (Global WACH).

References

- [1] UNAIDS, On the Fast-track to an AIDS Free Generation, UNAIDS, Geneva, 2016.
- [2] UNAIDS, Progress Report on the Global Plan, 2014.

- [3] M.P. Fox, S. Rosen, Retention of adult patients on antiretroviral therapy in low- and middle-income countries: systematic review and meta-analysis 2008–2013, *J. Acquir. Immune Defic. Syndr.* 69 (1) (2015) 98–108.
- [4] F.W. Kalemba, M. Zgambo, Loss to followup: a major challenge to successful implementation of prevention of mother-to-child transmission of HIV-1 programs in sub-Saharan Africa, *ISRN AIDS* (2012) 589817.
- [5] L. Tenthani, A.D. Haas, H. Tweya, A. Jahn, J.J. van Oosterhout, F. Chimbandira, et al., Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ('Option B+') in Malawi, *AIDS* 28 (4) (2014) 589–598.
- [6] M.H. Kim, S. Ahmed, M.C. Hosseinipour, T.P. Giordano, E.Y. Chiao, X. Yu, et al., Implementation and operational research: the impact of Option B+ on the antenatal PMTCT cascade in Lilongwe, Malawi, *J. Acquir. Immune Defic. Syndr.* 68 (5) (2015) e77–e83.
- [7] M.H. Kim, S. Ahmed, M.C. Hosseinipour, X. Yu, C. Nguyen, F. Chimbandira, et al., Brief report: impact of option B+ on the infant PMTCT cascade in Lilongwe, Malawi, *J. Acquir. Immune Defic. Syndr.* 70 (1) (2015) 99–103.
- [8] A.D. Haas, L. Tenthani, M.T. Msukwa, K. Tal, A. Jahn, O.J. Gadabu, et al., Retention in care during the first 3 years of antiretroviral therapy for women in Malawi's Option B+ programme: an observational cohort study, *Lancet HIV* 3 (4) (2016) e175–e182.
- [9] J. Dzangare, K.C. Takarinda, A.D. Harries, K. Tayler-Smith, M. Mhangara, T.M. Apollo, et al., HIV testing uptake and retention in care of HIV-infected pregnant and breastfeeding women initiated on 'Option B+' in rural Zimbabwe, *Tropical Med. Int. Health* 21 (2) (2016) 202–209.
- [10] M. Ngarira, E.A. Tarimo, H. Naburi, C. Kilewo, M. Mwanyika-Sando, G. Chalamilla, et al., Women's preferences regarding infant or maternal antiretroviral prophylaxis for prevention of mother-to-child transmission of HIV during breastfeeding and their views on Option B+ in Dar es Salaam, Tanzania, *PLoS One* 9 (1) (2014) e85310.
- [11] K. Clouse, S. Schwartz, A. Van Rie, J. Bassett, N. Yende, A. Pettifor, "What they wanted was to give birth; nothing else": barriers to retention in Option B+ HIV care among postpartum women in South Africa, *J. Acquir. Immune Defic. Syndr.* 67 (1) (2014) e12–e18.
- [12] H. Tweya, S. Guga, M. Hosseinipour, C. Speight, W. Ng'ambi, M. Bokosi, et al., Understanding factors, outcomes and reasons for loss to follow-up among women in Option B+ PMTCT programme in Lilongwe, Tanzania, *Trop. Med. Int. Health* 19 (11) (2014) 1360–1366.
- [13] A. Kagee, R.H. Remien, A. Berkman, S. Hoffman, L. Campos, L. Swartz, Structural barriers to ART adherence in Southern Africa: challenges and potential ways forward, *Glob. Public Health* 6 (1) (2011) 83–97.
- [14] O. Koole, J.A. Denison, J. Menten, S. Tsui, F. Wabwire-Mangen, G. Kwesigabo, et al., Reasons for missing antiretroviral therapy: results from a multi-country study in Tanzania, Uganda, and Zambia, *PLoS One* 11 (1) (2016), e0147309.
- [15] J. Thakkar, R. Kurup, T.L. Laba, K. Santo, A. Thiagalingam, A. Rodgers, et al., Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis, *JAMA Intern. Med.* 176 (3) (2016) 340–349.
- [16] S.H. Lee, U.B. Nurmatov, B.I. Nwaru, M. Mukherjee, L. Grant, C. Pagliari, Effectiveness of mHealth interventions for maternal, newborn and child health in low- and middle-income countries: systematic review and meta-analysis, *J. Glob. Health* 6 (1) (2016) 010401.
- [17] T.A. Gurman, S.E. Rubin, A.A. Roess, Effectiveness of mHealth behavior change communication interventions in developing countries: a systematic review of the literature, *J. Health Commun.* 17 (Suppl. 1) (2012) 82–104.
- [18] Perrier T, Dell N, DeRenzi B, Anderson R, Kinuthia J, Unger J, et al. Engaging pregnant women in Kenya with a hybrid computer-human SMS communication system. In: 33rd Annual ACM Conference on Human Factors in Computing Systems. pp. 1429–1438.
- [19] L.W. Porter, G.A. Bigley, R.M. Steers, *Motivation and Work Behavior*, seventh ed. McGraw-Hill/Irwin, New York, 2002.
- [20] N.K. Janz, V.L. Champion, V.J. Strecher, *The health belief model*, Health Behavior and Health Education Theory, Research, and Practice, third ed. Jossey-Bass, San Francisco, 2002.
- [21] T. Baranowski, C.L. Perry, G.S. Parcel, How individuals, environments, and health behavior interact. Social cognitive theory, Health Behavior and Health Education Theory, Research, and Practice, third ed. Jossey-Bass, San Francisco, 2002.
- [22] I.A. Beck, W. Deng, R. Payant, R. Hall, R.E. Bumgarner, J.J. Mullins, et al., Validation of an oligonucleotide ligation assay for quantification of human immunodeficiency virus type 1 drug-resistant mutants by use of massively parallel sequencing, *J. Clin. Microbiol.* 52 (7) (2014) 2320–2327.
- [23] D.S. Wald, S. Butt, J.P. Bestwick, One-way versus two-way text messaging on improving medication adherence: meta-analysis of randomized trials, *Am. J. Med.* 128 (10) (2015) 1139.e1–1139.e5.
- [24] R.T. Lester, P. Ritvo, E.J. Mills, A. Kariri, S. Karanja, M.H. Chung, et al., Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial, *Lancet* 376 (9755) (2010) 1838–1845.
- [25] H. Thirumurthy, N. Siripong, R.C. Vreeman, C. Pop-Eleches, J.P. Habyarimana, J.E. Sidle, et al., Differences between self-reported and electronically monitored adherence among patients receiving antiretroviral therapy in a resource-limited setting, *AIDS* 26 (18) (2012) 2399–2403.
- [26] A.K. Hall, H. Cole-Lewis, J.M. Bernhardt, Mobile text messaging for health: a systematic review of reviews, *Annu. Rev. Public Health* 36 (2015) 393–415.
- [27] K.J. Head, S.M. Noar, N.T. Iannarino, Harrington N. Grant, Efficacy of text messaging-based interventions for health promotion: a meta-analysis, *Soc. Sci. Med.* 97 (2013) 41–48.
- [28] T. Horvath, H. Azman, G.E. Kennedy, G.W. Rutherford, Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection, *Cochrane Database Syst. Rev.* 3 (2012), CD009756.
- [29] L.G. Park, J. Howie-Esquivel, K. Dracup, A quantitative systematic review of the efficacy of mobile phone interventions to improve medication adherence, *J. Adv. Nurs.* 70 (9) (2014) 1932–1953.
- [30] T.A. Odeny, E.A. Bukusi, C.R. Cohen, K. Yuhus, C.S. Camlin, R.S. McClelland, Texting improves testing: a randomized trial of two-way SMS to increase postpartum prevention of mother-to-child transmission retention and infant HIV testing, *AIDS* 28 (15) (2014) 2307–2312.
- [31] C. Evans, C.E. Jones, A.J. Prendergast, HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination, *Lancet Infect. Dis.* (2016).
- [32] E.N. Kurewa, F.Z. Gumbo, M.W. Munjoma, M.P. Mapingure, M.Z. Chirenje, S. Rusakaniko, et al., Effect of maternal HIV status on infant mortality: evidence from a 9-month follow-up of mothers and their infants in Zimbabwe, *J. Perinatol.* 30 (2) (2010) 88–92.
- [33] R. Hong, Association of maternal HIV infection with increase of infant mortality in Malawi, *J. Paediatr. Child Health* 44 (5) (2008) 291–296.
- [34] M.O. Omae, P.K. Langat, E.N. Ndung'u, Mobile subscription, penetration and coverage trends in Kenya's telecommunication sector, *Int. J. Adv. Res. Artif. Intell.* 4 (1) (2015) 1–7.
- [35] Organization WH, Guidelines on HIV and Infant Feeding. Principles and Recommendations for Infant Feeding in the Context of HIV and a Summary of Evidence, WHO, Geneva, 2010.
- [36] Towards the Elimination Of Mother-to-child Transmission of HIV and Keeping Mothers Alive in Kenya. A Strategic Framework 2012–2015. In: Nairobi: Kenya Ministry of Health; National AIDS and STI Control programme (NASCOP).
- [37] T.L. Clissold, W.G. Hopkins, R.J. Seddon, Lifestyle behaviours during pregnancy, *N. Z. Med. J.* 104 (908) (1991) 111–112.
- [38] The LifeWindows Project Team, The Life Windows Information Motivation Behavioral Skills ART Adherence Questionnaire (LW-IMB-AAQ), Center for Health, Intervention, and Prevention, University of Connecticut, 2006.
- [39] C.D. Sherbourne, A.L. Stewart, The MOS social support survey, *Soc. Sci. Med.* 32 (6) (1991) 705–714.
- [40] D. Rao, B.J. Feldman, R.J. Fredericksen, P.K. Crane, J.M. Simoni, M.M. Kitahata, A structural equation model of HIV-related stigma, depressive symptoms, and medication adherence, *AIDS Behav.* 16 (3) (2011) 711–716.
- [41] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, *J. Gen. Intern. Med.* 16 (9) (2001) 606–613.
- [42] J. McFarlane, B. Parker, K. Soeken, L. Bullock, Assessing for abuse during pregnancy. Severity and frequency of injuries and associated entry into prenatal care, *JAMA* 267 (23) (1992) 3176–3178.
- [43] J. Coates, A. Swindale, P. Bilinsky, Household food insecurity access scale (HFIAS) for measurement of household food access: indicator guide (v. 3) food and nutrition technical assistance project, academy for educational development, Food and Nutrition Technical Assistance Project, Academy for Educational Development, Washington, D.C, 2007.