Implementation science to expand an mHealth intervention for improving retention in care for women living with HIV and their children

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A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2016

Reading Committee:

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Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

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Introduction: The multi-step cascade of care for prevention of mother-to-child HIV transmission (PMTCT) paves the way to potentially eliminating mother-to-child HIV transmission; yet, it also lays the foundation for attrition and disengagement from care, increasing the risk of morbidity and mortality for both mother and child. We recently concluded a randomized controlled trial (RCT) in Kenya where we developed text messages using a behavioral theoretical framework and found that this "texting to improve testing" (TextIT) strategy significantly improved maternal retention in postpartum PMTCT care and rates of infant HIV testing. The goals of this dissertation were to understand "why" and "how" the intervention worked.

Methods: We conducted a "parallel cohort RCT" comparison of infant HIV testing rates in RCT non-participants (reference category) versus control, and intervention group participants (chapter 2). We also conducted a cluster-randomized, stepped-wedge trial in western Kenya to determine the real-world effect of TextIT on infant HIV testing within eight weeks after birth (chapter 3), and maternal retention in postpartum HIV care (chapter 4).

Results: Chapter 2: Compared to trial-ineligible participants, women in the control group of the TextIT RCT (hazard ratio [HR] 2.82; 95% CI 2.29–3.48) and the trial SMS group (HR 3.48; 95% CI 2.84–4.27) were more likely to have their infants tested for HIV. Chapter 3: A greater proportion of infants in the intervention group received HIV testing compared with the standard care group, but the difference was small, and not statistically significant (relative risk [RR] 1.05; 95% CI 0.98–1.12; p=0.2). Chapter 4: TextIT led to a significant improvement in postpartum retention in PMTCT compared to standard care (RR 1.18; 95% CI 1.01–1.39; p=0.04)

Conclusions: The combined results of Chapters 2 and 3 could be interpreted as showing that simply paying more attention to infant HIV testing within PMTCT programs can achieve fairly high rates of testing even without the SMS part of the intervention. The results in Chapter 4 go a step further, showing that the SMS component of the intervention can be a powerful adjunct to a functional health system to bolster maternal retention in early postpartum PMTCT care.

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ACKNOWLEDGEMENTS

First, I would like to sincerely thank my dissertation committee chair and mentor, Dr. R. Scott McClelland, who graciously took me under his wings seven years ago, and patiently nurtured me in science since. Scott has not only been an outstanding scientific mentor providing critical feedback and much-needed guidance, but an exceptional model for achieving a work-family balance. I continue to look up to him as a role model for what I would like to become as a researcher – a scientist with a strong work ethic, a thorough physician, a selfless mentor, and a committed family man.

I am grateful to Dr. King Holmes, whose recommendation enabled me join the University of Washington's MPH program, and who continues to encourage and enthusiastically support me through the journey. A renaissance man, King's conversations always teach me something new. I thank Prof. James Hughes for his gentle introduction to biostatistics when I joined the MPH program. As a world-leading expert in designing and analyzing stepped-wedge trials, Jim's willingness to serve on my supervisory committee was a godsend. I thank Dr. Elvin Geng, one of the smartest people I have ever met, for his steadfast friendship and support. Elvin is an exceptional scientist and outstanding physician, yet humble to a fault. He has gone out of his way to support my growth as a physician-scientist, creating endless opportunities for my development, and teaching me a tremendous amount about epidemiology, implementation science, and life. He has been like a big brother that I never had. My heartfelt gratitude to Prof. Elizabeth Bukusi, a mentor extraordinaire, who has been at the forefront of my development as a young scientist and continues to steadfastly support me and my wife through our professional and family life. Thank you Prof. EB, for being always available, ever caring, and forever loving; for continuing to be a source of professional and personal inspiration for us; and for being the embodiment of the all-round mentor. Thank you also for providing the platform for this research through the FACES organization you co-founded and lead.

I am also grateful to our family friends who have supported us through the journey, with special thanks to Carol and Dave Anderson, Danita and Gary Talbert, and Krista Yuhas. I also thank the International AIDS Research and Training Program (IARTP) family, who funded me through my early training and continue to support me: Carey Farquhar, Eileen Seese, Rowena de Saram, Tammy Wilson, Britt Sylvester, Lindsay Mumm, Michelle Mooney, and Nicole Hobbs. I thank Eliud Akama and the TextIT study team for their dedication and invaluable contribution to this work.

I remain grateful to my family; my late father whose sacrifices in life got me where I now am; and my mother for her constant prayers. Most of all, I thank my wife Beryne Odeny, my pillar of strength who has believed in me and stood by me through it all.

Finally, I thank God for the gift of life, the opportunity to begin and complete this amazing journey, and His blessings that are new every morning.

DEDICATION

To Aaron Jaler Odeny. May you shine before men, that they may see your good works, and glorify our Father which is in heaven. Matthew 5:16

To my nephew, Lumumba Jr., who fought the brave fight for all 12 months of his life, and inspired me in more ways than he would ever know.

And, as always, to Beryne Odeny: pillar of strength, woman without limits, and loving companion in the journey of life. Thank you for your love, support, encouragement, and dedication.

Chapter 1. INTRODUCTION

1.1 PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV

In 2011, the Joint United Nations Programme on HIV/AIDS (UNAIDS), launched the *Global Plan towards the elimination of new HIV infections among children and keeping their mothers alive* (Global Plan) with the goals of reducing the number of new HIV infections among children by 90%, and reducing the number of AIDS-related maternal deaths by 50% [1]. The Global Plan focused on 22 "priority" countries (21 in sub-Saharan Africa plus India) that accounted for 90% of HIV-infected pregnant women. In 2009, the baseline year for the Global Plan, the estimated number of new HIV infections among children in the 21 priority sub-Saharan African countries was 330,000 [2]. Since then, a number of interventions have led to a rapid decline in HIV incidence among children. In 2014, the number of new HIV infections among children in the 21 priority sub-Saharan African countries had declined by about half, to 170,00 children [3]. The most visible intervention has been the provision of antiretroviral therapy (ART) to pregnant and breastfeeding women living with HIV. There was a remarkable increase in the proportion of HIV-infected pregnant women receiving ART from 37% in 2009 to 77% in 2014. As a result, an estimated 1.1 million new HIV infections among children have been averted, and AIDS-related deaths among HIV-infected pregnant women have declined by 45% [3]. In 2015, the World Health Organization (WHO) recommended providing lifelong ART to all HIV-infected pregnant and breastfeeding women, regardless of CD4 cell count [4]. This guideline, previously dubbed "Option B+", is expected to lead to even greater declines in both the number of new HIV infections and AIDS-related maternal deaths.

Despite the rapid decline in HIV incidence among children and AIDS-related mortality among women of reproductive age, priority countries are still far from achieving the ambitious goals of the Global Plan. The average 48% decline in new infections across priority countries is encouraging, yet progress in individual countries remains heterogeneous, ranging from a 15% decline in Nigeria to as much as a 76% decline in South Africa [3]. Nonetheless, the overall rate of mother-to-child HIV transmission in the 21 African priority countries remained high, at 14% in 2014 [5]. The cascade of care for women living with HIV and their babies includes retention in prevention of mother-to-child transmission (PMTCT) programs through pregnancy and the postpartum period, and early infant diagnosis (EID) of HIV. Navigating this cascade of care can be complex, due to the different and changing needs of the woman and her infant at each step. First, a pregnant woman must understand that ART plays a dual role, treating her HIV infection and preventing transmission to her unborn baby. Second, she needs to ensure that her baby receives antiretroviral prophylaxis for at least six weeks after delivery. Third, her baby needs to undergo HIV virologic testing at six weeks. If the test result is positive, subsequent care would include prompt ART initiation. If negative, the baby would need close follow-up and HIV antibody testing at 18-24 months. Finally, mothers are required to adhere to clinic appointments and medication, to carefully consider the decision to breastfeed or not, and to remain continuously engaged in care [6]. This complex and precarious path has resulted in high rates of loss to follow-up during pregnancy and after delivery among pregnant HIV-positive women in sub-Saharan Africa [7]. Much remains to be done to keep mother-baby pairs fully engaged in PMTCT.

1.2 Great Potential of the PMTCT Cascade for Mothers Is Not Always Realized

Despite the benefits of maternal ART for PMTCT, many pregnant women living with HIV still do not access ART services. The Option B+ approach was designed in part to reduce barriers to ART initiation for pregnant and breastfeeding women, such as complex treatment regimens and the need for CD4 testing to determine treatment eligibility. However, among the priority countries, only 77% of eligible women are estimated to be receiving ART for PMTCT, and even less (66%) are on lifelong treatment (Option B+) [3]. In one analysis of four hospitals in Kenya, only 20% of women who met the recommended Option B+ guidelines for ART initiation in the PMTCT program actually received ART [8]. Among women who initiate ART and are later transferred from PMTCT clinics in the postpartum period to general adult ART clinics, about 25% disengage from care after referral [9]. The less than perfect treatment coverage for HIV-infected pregnant women, combined with high attrition at the point of transfer to general ART clinics, reflect the precarious steps along the cascade of care and treatment for pregnant and breastfeeding women living with HIV. The multi-step PMTCT cascade means that the great potential of this strategy for preserving the health of mother and their infants is not always realized. It paves the way to achieving virologic suppression and potentially eliminating mother-to-child HIV transmission; yet, it also lays the foundation for attrition and disengagement from care, increasing the risk of morbidity and mortality for both mother and child.

The complexity of factors that influence women's success or failure in the PMTCT cascade is perhaps best highlighted in Malawi's pioneering Option B+ program. In this program, pregnant women who initiated ART for PMTCT had a five-fold higher risk of failure to return to clinic compared to those who started ART for their own health [10]. Retention in PMTCT in this

program has varied between 65% and 87% [10-13]. A similar picture of imperfect engagement in care is observed across other sub-Saharan African Option B+ programs: 88% retained at 6 months in Ethiopia [14], 83% retained at 6 months in Zimbabwe [15], 66% retained at one year in Ghana [16], and 66% completing post-natal follow-up in Nigeria [17]. A systematic review and meta-analysis of 44 studies from 15 sub-Saharan African countries reported significant drop-offs along the cascade of PMTCT care for mother-baby pairs: 70% of HIV positive pregnant women received antiretroviral prophylaxis, 64% of HIV-exposed infants were tested for HIV using DNA PCR at six weeks after birth, and 55% were tested between one year and 18 months of age [7].

1.3 The PMTCT Cascade for Infants

The WHO recommends daily antiretroviral prophylaxis for 4-6 weeks for all infants born to HIV-infected women, followed by HIV virologic testing at six weeks of life [18]. Thereafter, the treatment cascade bifurcates based on the result of the infant's virologic test. HIV-positive infants receive immediate ART and remain in lifelong care, with the aim of achieving virologic suppression and long-term survival. HIV-negative infants receive follow-up care that is tailored based on whether they were ever breastfed. Infants whose virologic tests are negative at six weeks and who never breastfed are considered uninfected, while those who breastfed are considered to be at ongoing risk of acquiring HIV. For breastfeeding children, HIV testing is repeated at 9 months using antibody-based tests. Positive antibody-based tests are confirmed using a virologic test, and infants whose virologic tests turn positive are started on immediate ART. Children whose antibody tests are negative at 9 months (or positive but with a subsequent negative confirmatory virologic test) are required to undergo repeat antibody testing at 18

months of age or 3 months after cessation of breastfeeding [18]. The aim of follow-up, for these children, is HIV-free survival at 18 months [6].

Without treatment, infants who acquired HIV infection perinatally have an estimated 52% probability of death in the first year of life [19]. Early diagnosis and prompt initiation of ART among infants reduces mortality by 76% [20]. Of the 2.1 million children living with HIV in the 21 priority countries, 31% were receiving ART in 2014, up from 10% in 2009 [5]. While encouraging, this proportion was far below the ART coverage for adults in 2014 (40%), and means that a substantial number of infants suffer high morbidity and mortality. This gap in infant treatment initiation highlights the need for, and difficulty of, retaining children in care through the PMTCT cascade.

1.4 Leakage Along the Cascade of Care for Infants

Sub-Saharan Africa bears the greatest burden of HIV in children. Of the 2.6 million children living with AIDS in 2014, 2.3 million (88%) lived in sub-Saharan Africa [5]. The introduction of WHO Option B+ treatment guidelines has led to improvements in treatment outcomes for children in sub-Saharan Africa, including reductions in infant HIV acquisition [21, 22]. However, low engagement of infants at various points along the cascade of care and treatment poses a significant threat to the success of PMTCT programs. For example, although early infant ART is well established as the cornerstone for limiting morbidity associated with HIV, programmatic bottlenecks in early infant diagnosis make it difficult to achieve the best outcomes for HIV-exposed infants [23]. In 2014 only 49% of an estimated 1.2 million infants born to HIV-positive mothers in the 21 priority sub-Saharan African countries were tested for HIV using a virologic test within the recommended six weeks [3]. No clear data exist to document the proportion of HIV-exposed children tested for HIV at 18 months of age or at cessation of

breastfeeding. Moreover, despite the WHO recommendation to start ART in all children living with HIV [4], only 31% were receiving ART by the end of 2014 [3].

A recent systematic review found high levels of loss to follow-up among infants born to HIV-infected women in sub-Saharan Africa, including 34% lost within 3 months of delivery and 46% lost after HIV virologic testing [24]. Among children who undergo HIV virologic testing, a substantial proportion either do not get linked to timely HIV treatment services or disengage from care after linkage for a number of reasons [25]. First, parents or guardians may fail to return for test results. For example, only 55% of parents/guardians in Tanzania returned to collect virologic test results for their HIV-exposed infants [26]. Second, infants determined to be HIV-positive may be lost to follow-up after receiving results of HIV virologic testing but before linkage to HIV treatment services. In South Africa only 54% of HIV-infected infants were linked to pediatric HIV services, while only 30% were referred for care and treatment in Malawi [27, 28]. Third, delays in transmitting test results to facilities and caregivers may lead to late ART initiation. In Malawi, despite improvements in timely infant HIV virologic testing, the median age at ART initiation was 16 weeks [21]. Mortality among infants infected with HIV peaks 2-3 months after birth [29], and late ART initiation may not be adequate to prevent HIV disease progression [30]. Finally, among children successfully linked to HIV treatment services, there are high levels of loss to follow-up (LTFU). A large pediatric HIV treatment cohort in Tanzania reported 34% LTFU (defined as having the last clinic visit more than 90 days prior if on treatment, or more than 180 days prior if not receiving ART) [31]. Another study in three regions of Tanzania reported 61% LTFU among infants receiving ART [32]. In rural Malawi, 39% of children initiating ART were LTFU [33]. Outcomes among LTFU children include death,

disengagement from care, and transfers out. In urban Malawi, tracing of LTFU children found that 11% had died, 25% had stopped taking ART, and 26% had transferred out [34].

Although there has been much progress toward elimination of new HIV infections among children and keeping their mothers alive, much more remains to be done to sustain the gains and eliminate mother-to-child HIV transmission. The "leaks" along the PMTCT cascade for children illustrate the need for public health practitioners to urgently develop efficacious, cost-effective, and sustainable interventions to close the gaps. In response, innovative strategies are being developed targeted to different gaps along the cascade (Table 1.1).

A 2016 systematic review of 34 studies describing interventions to improve outcomes along the continuum of PMTCT care, including 19 interventions targeting early infant diagnosis, concluded that only mobile-phone based text messages were effective in increasing rates of early infant HIV testing [35]. Another 2016 systematic review of interventions to improve postpartum retention of women in PMTCT found evidence that phone-based interventions led to improvements in retention in the early postpartum period [36].

1.5 Closing Gaps in PMTCT Retention using mHealth

The increase in number of mobile phone connections in sub-Saharan Africa has been spectacular, presenting a unique opportunity to add mobile technology for health (mHealth) to the armamentarium for turning the tide of HIV. For example, one survey found that 100% of Kenyan health workers owned a mobile phone and 99% used short message service (SMS) text messaging [37]. Consequently, a new generation of interventions using mHealth are being developed, tested, and implemented across Africa to extend the frontiers of using technology to support HIV prevention, care, and treatment. These interventions span the spectrum of complexity from simple text messages to sophisticated social networking applications. They

target both health care providers and their clients, and apply across the continuum of HIV care from prevention through lifelong treatment. However, few are specifically targeted at closing the gaps along the PMTCT cascade for pregnant and breastfeeding mothers living with HIV and their infants (Table 1.2). While many of these studies were well designed, few provide strong and actionable evidence that mHealth approaches can improve postpartum PMTCT retention and early infant HIV testing. In addition, studies using text messaging targeted at behavior change to improve aspects of PMTCT generally have not included a firm foundation in health behavior theories [38]. As a result, it is difficult to determine whether these approaches would be replicable in other settings.

We recently concluded a successful randomized controlled trial (RCT) in Kenya entitled, "Improving uptake of early infant diagnosis of HIV for PMTCT: a randomized trial of a text messaging intervention" (ClincalTrials.gov #NCT01433185) [39]. In this trial, we developed text messages using a behavioral theoretical framework [40]. We found that this "texting to improve testing" (TextIT) strategy significantly improved maternal attendance at postpartum clinic appointments and rates of testing to facilitate early infant diagnosis of HIV. Interestingly, the testing rate in the control group (85%) was much higher than the expected rate in the broader clinic population from which the study sample was obtained (37%). With these results demonstrating efficacy, the goals of this dissertation were to understand "why" and "how" the intervention worked. These data will be used to inform future expansion of this mHealth strategy. In the first aim, we directly measured the difference in infant HIV testing rates among study participants in the control group versus the group screened but not enrolled in the trial. To do this, we used prospectively collected programmatic data and conducted a comparison of RCT non-participants (reference category) versus control group participants and intervention group

participants. Goldenberg et al. have previously described this "parallel cohort RCT" design [41]. In this design, patients ineligible for randomization in a clinical trial are evaluated in a parallel cohort arm to maximize use of information from the background population of interest.

To understand the strengths and limitations of the TextIT intervention in a routine-care setting, we conducted a cluster randomized, stepped wedge trial in 20 clinics operated by the Ministry of Health in the Nyanza region of Kenya. We aimed to determine the effect of TextIT on infant HIV virologic testing within eight weeks after birth (aim 2), and maternal retention in postpartum HIV care (aim 3). We hypothesized that infants at health facilities implementing TextIT will be more likely to have HIV virologic testing compared to infants at health facilities implementing standard care. We also hypothesized that a greater proportion of women at health facilities implementing TextIT will attend clinic within eight weeks postpartum compared to women at health facilities implementing standard care.

Given the urgent goal of elimination of mother-to-child transmission of HIV, our phased and systematic approach to understanding and expanding the TextIT strategy will be an important step toward the ultimate aim of reaching countrywide scale-up. Understanding the strengths and limitations of this intervention in a real-world, routine-care setting represents the next step in the translational pathway to public health impact. The TextIT strategy thus maps well onto the stages of translational epidemiology as described by Khoury et. al [42] (Figure 1.1). This "implementation science" approach to translating research findings into routine practice has been promoted as key to success in the global response to the HIV/AIDS epidemic [43-46].

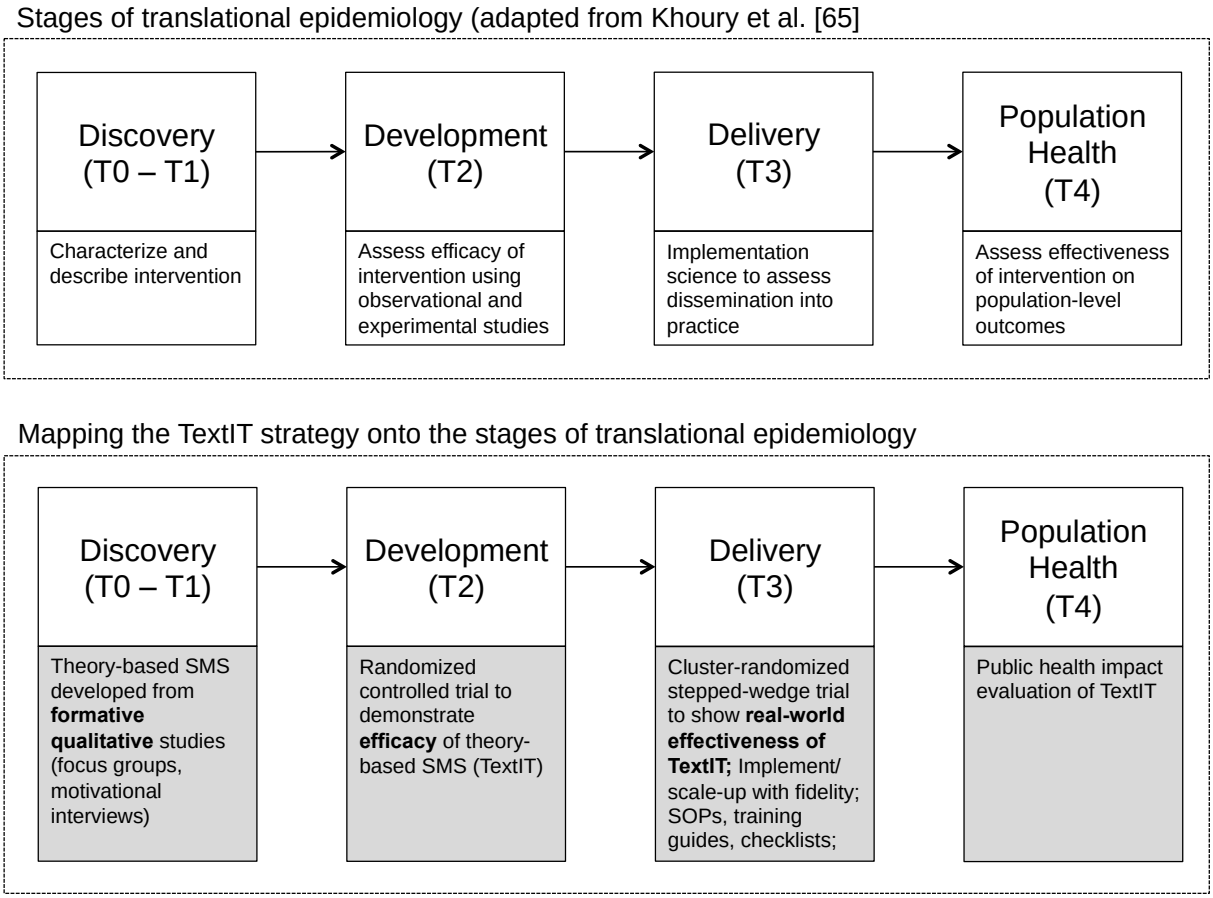

Figure 1.1. Mapping the TextIT strategy onto the stages of translational epidemiology.

Table 1.1. Emerging innovative strategies to bridge gaps along the PMTCT cascade for infants.

Gap	Strategy	Location
1. Low proportion of HIV-positive infants identified at 6 weeks of age and initiated on timely ART	HIV virologic testing at birth to increase the percentage of HIV-positive infants identified and initiated on timely ART [47, 48].	South Africa
2. Low uptake of early infant HIV testing at the recommended 6 weeks	Mobile phone text messages to pregnant and breastfeeding women to increase uptake of early infant HIV diagnosis [39, 40].	Kenya
3. Transport and infrastructural challenges that delay HIV virologic testing and return of test results	Point-of-care virologic tests to provide same-day results[49, 50].	Mozambique, South Africa
	Mobile phone text messages to reduce turn-around-time for delivering virologic test results to health facilities [51].	Zambia
4. Poor coordination of maternal and infant HIV services with routine child health clinics	Optimizing clinic attendance for mother-baby pairs by aligning HIV care visits with immunization schedules [52-55].	Tanzania, Zimbabwe, South Africa
5. Low proportion of children living with HIV identified and linked to treatment services	Task shifting of in-hospital HIV testing tasks from nurses to trained lay counselors [56].	Malawi
	Using community health workers to provide HIV counseling, testing, and linkage services [57, 58].	Malawi
6. Poor retention of HIV-infected women in postpartum HIV care	Mobile phone text messages to pregnant and breastfeeding women[39, 40].	Kenya
7. Low retention of HIV-exposed and HIV-infected infants in follow-up care	Mobile phone reminders to improve follow-up care for HIV-exposed or infected infants [59].	Cameroon
8. Low rates of ART initiation among HIV-infected infants	Web-based technologies to improve ART initiation for HIV-infected infants [60].	Kenya

PMTCT=prevention of mother-to-child HIV transmission; ART=antiretroviral therapy.

Table 1.2. Mobile phone based interventions to close gaps along the PMTCT cascade for infants.

Author and year	Location	Intervention	Objective	Study period
Finocchario-Kessler 2014 [60]	Kenya	SMS alerts to mothers of HIV-infected infants	Increase retention in postpartum PMTCT and rates of infant ART initiation	April 2011 to May 2012
Kebaya et al. 2014 [61]	Kenya	2-weekly mobile phone calls	Improve retention in care for HIV-exposed infants	Unknown
Odeny et al. 2014 [39]	Kenya	Two-way text messaging	Increase postpartum retention and rates of infant HIV testing	April 2012 to October 2012
Mwapasa et al. 2014 [62]	Malawi	SMS based notifications to community health workers for mothers who miss scheduled clinic appointments	Improve retention of mother-infant pairs in PMTCT	May 2013 to ongoing
Deo et al. 2015 [63]	Mozambique	Expedited results delivery system using text message based printers	Communicate results of infant HIV test to facilities	2008 to 2010
Mushamiri et al. 2015 [64]	Kenya	A text message based system to facilitate and coordinate community health worker activities for ANC and PMTCT	Improve adherence to ANC and PNC clinic visits	October 2010 to April 2011
Schwartz et al. 2015 [65]	South Africa	SMS and phone calls through six weeks postpartum	Improve retention of mother-infant pairs in PMTCT	May 2013 to July 2013
Peter et al. 2016 [66]	South Africa	Mobile application (“app”) containing HIV treatment guidelines for clinicians	Provide HIV treatment guidelines, calculate pediatric drug dosages, and report drug stock-outs	June 2015

ANC=antenatal care; PMTCT=prevention of mother-to-child HIV transmission; ART=antiretroviral therapy; SMS=short message service.

Chapter 2. THE SISYPHEAN TASK OF INCREASING AND SUSTAINING INFANT HIV TESTING RATES

2.1 INTRODUCTION

The proportion of HIV-exposed infants in sub-Saharan Africa who undergo HIV testing within two months of birth (49%) is low. However, there is substantial heterogeneity across countries, ranging between 4% in Nigeria and >95% in Namibia [3]. In Kenya, a reported 72% of eligible infants underwent testing within 2 months of birth in 2014. In one of the largest PMTCT programs in Kenya, Family AIDS Care and Education Services (FACES), trends in the proportion of infants receiving early HIV testing have been fluctuating over time. For example, in 2010, 46% of eligible infants received HIV virologic testing. This proportion rose sharply to a peak of 87% in 2011 [67]. In 2012, there was a massive reduction to only 43% of eligible infants receiving virologic testing [68]. It appeared that efforts to increase uptake produced positive results, but that increases were not sustained when these targeted programs ended.

In response to this Sisyphean dilemma, we developed and evaluated the TextIT intervention, broadly aimed at increasing and sustaining uptake of infant HIV testing within the FACES PMTCT program. We found that the TextIT intervention significantly improved rates of infant HIV testing. We also observed, unexpectedly, that the proportion of women in the control group whose children received virologic HIV testing was substantially higher than the background proportion among other women attending PMTCT at FACES, including those screened but not enrolled in the TextIT trial. The informed consent process for this trial included a one-on-one session between a study staff member and potential participant to recapitulate the importance of remaining engaged in PMTCT. We hypothesized that this process, which is not a component of routine PMTCT care, may have led to higher rates of infant HIV testing among

control group women versus ineligible women. To address this question, we compared outcomes in HIV-infected pregnant women screened but not enrolled in the trial to those of trial participants. We hypothesized that there would be progressive stepwise increases in infant HIV testing rates when comparing non-participants (reference category) to infants in the control and intervention groups of the trial.

2.2 METHODS

2.2.1 *Design and Participants*

In this "parallel-cohort RCT" analysis [41], the primary exposure was participation in the randomized trial that determined the efficacy of the TextIT strategy. The TextIT study was a RCT to evaluate the effect of two-way text messages in increasing postpartum PMTCT retention and rates of infant HIV testing in Kenya. The design, analysis, and results of the trial are presented elsewhere [39, 40]. Briefly, HIV-infected pregnant women in PMTCT programs were randomly assigned to receive either theory-based two-way text messages during pregnancy and the postpartum period (intervention arm) or usual care (control arm). Inclusion criteria for the trial included: 1) adult 18 years or older; 2) gestational age of 28 weeks or greater (or having delivered on the day of enrollment); 3) enrolled in the PMTCT program at FACES; 4) planning to remain in study area; 5) having access to a mobile phone; and 6) reporting ability to read or have someone who reads short message service (SMS) on potential participant's behalf. Women who reported sharing phones were ineligible unless they had disclosed their HIV status to the person sharing the phone. The primary trial outcome was the proportion of infants undergoing HIV virologic testing, assessed using an intention-to-treat analysis. Ethical review committees of

the Kenya Medical Research Institute, University of Washington, and University of California San Francisco approved the trial. All participants provided written informed consent.

Women who were recruited and screened for the randomized trial but did not meet criteria for inclusion were selected as the comparison group for this analysis. The primary outcome for this secondary analysis was time to infant HIV testing, defined as obtaining a dried blood spot sample for HIV virologic testing within 8 weeks after birth.

2.2.2 *Study Procedures*

Baseline demographic characteristics for participants enrolled in the trial were collected using a questionnaire administered prior to randomization. Baseline demographic characteristics for participants screened but not enrolled were extracted from retrospective review of trial screening logs, patient charts, antenatal care clinic registers, and electronic medical records. Follow-up and primary outcome information for both trial and non-trial participants were ascertained from several data sources, including the HIV-exposed infants (HEI) register, HEI patient chart, health facility maternity register, postnatal clinic register, and PMTCT clinic patient charts.

2.2.3 *Statistical Analysis*

In descriptive analyses, we compared the distribution of baseline socio-demographic and clinical characteristics across three groups using chi-square tests. These three groups were trial participants in SMS arm (Trial SMS), trial participants in control arm (Trial Control), and women screened but not enrolled in the trial (Ineligible). The population for primary analysis comprised all trial and non-trial participants with baseline data.

We analyzed time to infant HIV testing comparing Trial SMS, Trial Control, and Ineligible participants using the Kaplan-Meier method and log-rank tests. We also fit a Cox

proportional hazards regression model to estimate hazard ratios and associated 95% confidence intervals (CI) comparing time to infant HIV testing for the three groups. We chose this outcome because infants may be brought to clinic earlier or later than the scheduled appointment. In this case, a time to event analysis would enable an understanding of both rate and timeliness of infant HIV testing. Time to infant HIV testing was measured in days from the date of birth to the date when a dried blood spot (DBS) sample was collected for HIV virologic testing. In routine practice, DBS samples are collected six weeks after birth to coincide with infant immunization clinic schedules. However, DBS collection between birth and six weeks would still be valid for determining infant HIV status. Therefore, we included this initial period in our survival analysis to capture any testing events that might have occurred prior to the six-week immunization visit. Survival time was censored at eight weeks or at the time of maternal or infant death. We assessed the proportional hazards assumption using tests and graphs based on scaled Schoenfeld residuals.

Potential confounding factors were included in the final regression model using a sequential approach. We implemented a two-step version of the method proposed by Evans et al. [69] and Weng et al. [70] for combining prior background knowledge (using directed acylic graphs) and statistics-based methods to determine adjustment variables. First, we applied subject-matter knowledge to identify variables for model inclusion based on *a priori* importance of being risk factors or potential confounders of the association between trial participation and infant HIV testing [71]. These variables included trial eligibility criteria, education level, receiving ART for own health, year of enrollment into PMTCT, knowledge about PMTCT, receiving ART prophylaxis for PMTCT (AZT during pregnancy, AZT+3TC+NVP at delivery, AZT+3TC after delivery, and infant NVP), and fear of discrimination. The relationships between these variables were summarized and analyzed qualitatively using a directed acyclic graph

(DAG) as shown in Figure 2.1 [72]. Based on this DAG, age, education, and enrollment in PMTCT were determined to be sufficient for adjustment to control for confounding.

Second, we refined the list of factors for inclusion in the model by fitting a Cox proportional hazards model with a forward stepwise model building approach. We retained variables that changed the estimated hazard ratio of the main effect by ≥10% [73]. We found this stepwise model selection approach appropriate in this instance because it generally results in selection of all important confounding factors, even though some selected variables may not be confounders [71]. The initial multivariable regression model is shown below:

$$\lambda(t|X) = \lambda_0(t) \cdot \exp(\beta_1 StudyArm + \beta_2 Adult + \beta_3 Education + \beta_4 PMTCT) \quad (2.1)$$

In this model, $\lambda(t|X)$ is the hazard of infant HIV testing at time t given a vector of covariates X, and $\lambda_0(t)$ is the baseline hazard. This initial model included four covariates: *StudyArm* is a categorical variable for exposure group (0=Ineligible; 1=Trial Control; 2=Trial SMS); *Adult* is a binary variable for whether a woman was ≥18 years old or <18 years old at baseline; *Education* is a categorical variable for level of education (0=None; 1=Primary; 2=Secondary; 3=Post-secondary); *PMTCT* is a binary variable for whether a woman was enrolled in the PMTCT program at baseline. After applying the stepwise approach, we dropped both *Adult* and *Education* from the model as the estimate of the hazard ratio did not change regardless of their inclusion. Therefore, the final model adjusted only for enrollment in PMTCT.

To investigate whether results were biased by the high proportion of non-trial participants without outcome information, we performed sensitivity analyses that considered them all first as failures, and then as successes. The multivariable regression models for these sensitivity analyses were unadjusted, given that non-trial participants without outcome information were also missing

baseline demographic and clinical characteristics. We decided against using multiple imputation for missing baseline and outcome information, due to the high proportion of missingness among non-trial participants and the implausibility of the assumptions that the data were either missing completely at random (MCAR) or missing at random (MAR). We considered the use of a missing indicator category to increase statistical power but dropped it in favor of a complete case analysis due to the unpredictable bias inherent with this method [74, 75]. We concluded that a complete case analysis would yield unbiased estimates because missingness of baseline covariates was likely independent of the outcome of infant HIV testing [76, 77].

We report unadjusted and adjusted hazard ratios and corresponding 95% confidence intervals. All tests were two-sided and significance level of $P < 0.05$ was used. We used Stata v13 to perform all statistical analyses (StataCorp, College Station, TX).

2.3 RESULTS

2.3.1 *Study participants*

There were 1,324 screening visits by 1,115 HIV-positive pregnant women attending antenatal clinic between April and October 2012, including those not enrolled in the FACES PMTCT program (Figure 2.2). Of these, 388 women were eligible for trial enrollment and were randomized to receive the intervention text messages (N=195) or continue usual care (N=193). The remaining 727 women were ineligible for trial enrollment for various reasons, including 550 (76%) with gestation <28 weeks and 170 (23%) who did not have access to a phone (Figure 2.3). Among those ineligible for the trial, 217 patient records could not be located. This precluded ascertainment of both their baseline and follow-up information. Source documents (antenatal clinic register, patient clinic chart) were completely missing for 193/217 (89%). Clinic identifiers collected at screening for the remaining 24 women (11%) could not be linked with any other

record, including health facility registers and patient charts. Reasons for failure to link records included patients reporting clinic identifiers issued at non-study facilities, relevant pages on clinic registers being torn or illegible, and errors in transcription of clinic identifiers during screening. Trial eligibility criteria did not differ significantly between these 217 women without clinic records compared to other ineligible women whose records were available (Table 2.3).

Baseline characteristics comparing trial participants versus those ineligible (excluding the 217 without baseline records) are shown in Table 2.4. Overall, among the 898 patients with data available (388 trial participants and 510 ineligible women) the median maternal age at screening was 26 years (interquartile range [IQR] 23–30), 110 (12%) were employed, 540 (60%) had primary or greater level of education, 760 (11%) were married, and 148 (16%) were primigravidae. The median CD4 cell count at screening was 459 cells/μL (IQR 320–620), 151 (17%) were classified as having WHO stage 3 or 4 disease, and 424 (47%) were receiving ART for their own health.

Ineligible women had high proportions of missing data across all baseline variables (Figure 2.4). However, the distribution of maternal age, employment status, gravidity, parity, WHO clinical stage, most recent CD4 cell count, and reason for being on ART (own health versus PMTCT prophylaxis) did not differ significantly when compared with trial participants (Table 2.4). There were higher proportions of women with primary or greater level of education in the trial SMS and control groups compared to the ineligible group (98%, 99%, and 31% respectively; $p<0.01$). The proportion of married women was two times higher in the trial SMS and control groups compared to those ineligible for the trial (15%, 16%, and 8% respectively; $p<0.01$). There were statistically significant differences comparing trial and ineligible participants whose records indicated receiving components of the WHO Option A prophylaxis

medications for PMTCT. These included AZT during pregnancy (42% for trial SMS, 44% for trial control, 47% for ineligible; p<0.01); AZT+3TC+NVP during delivery (28% for trial SMS, 31% for trial control, 47% for ineligible; p<0.01); AZT+3TC after delivery (26% for trial SMS, 31% for trial control, 47% for ineligible; p<0.01); or infant nevirapine prophylaxis (69% for trial SMS, 71% for trial control, 75% for ineligible; p<0.01).

2.3.2 *Time to infant HIV testing*

Overall, the median time from birth to infant HIV testing was 43 days (95% CI 43–44). The Kaplan-Meier estimates of the cumulative probability of infant HIV testing were highest among trial participants in the SMS group (92.0%; 95% CI 87.5–95.3), followed by trial participants in the control group (85.1%; 95% CI 79.5–89.8), and lowest among women screened but not enrolled in the trial (43.4%; 95% CI 39.2–47.8) (log-rank p-value<0.0001; Figure 2.5). This progressive stepwise increase in the cumulative proportion of infants receiving HIV virologic testing across the three groups demonstrated a statistically significant linear trend (Tarone trend test p<0.001). There was a stepwise increase in the adjusted hazard ratios of infant HIV testing when comparing the ineligible group with the trial control group (hazard ratio [HR] 2.82; 95% CI 2.29–3.48), and with the trial SMS group (HR 3.48; 95% CI 2.84–4.27) (Table 2.5).

2.3.3 *Determinants of the rate of infant HIV testing*

In Cox proportional hazards models (Table 2.5), having a gestational age greater than 28 weeks at the time of screening was significantly associated with higher rates of testing (HR 2.29; 95% CI 1.91–2.75). There was a statistically significant stepwise increase in the rates of infant HIV testing with increasing maternal age. Compared to women younger than 18 years, there were higher rates of infant HIV testing in women aged 18-24 years (HR 3.38; 95% CI 0.84–13.64;

p=0.09), 25-34 years (HR 4.24 95% CI 1.06–17.04; p=0.04), and older than 35 years (HR 5.77; 95% CI 1.41–23.56; p=0.02). Similarly, higher education levels were associated with a stepwise increase in rates of infant HIV testing. Compared to women who reported no education, women who had primary education had a hazard ratio of 1.63 (95% CI 0.95–2.80; p=0.07), those with secondary education had a hazard ratio of 1.69 (95% CI 0.97–2.96; p=0.04), and those with post-secondary education had a hazard ratio of 2.16 (95% CI 1.19–3.94; p=0.01). Women who were tested for HIV on the day of screening for trial enrollment were also significantly more likely to have their infants tested for HIV compared to those who had been tested earlier (HR 2.06 95% CI 1.49–2.85; p<0.001). Women who had a record of having received ART for their own health (either as part of the WHO Option B guideline or prior to pregnancy) were also significantly more likely to have their infants tested for HIV compared to those not receiving ART for their own health (HR 1.44; 95% CI 1.21–1.71).

2.3.4 *Sensitivity analysis*

The Kaplan-Meier plots of cumulative probabilities of infant HIV testing demonstrating the range of sensitivity analysis are shown in Figure 2.6. When the 217 ineligible women whose clinic files could not be located to determine baseline data or study endpoints were all treated as failing to receive infant HIV testing, the cumulative probability of infant HIV testing among all trial ineligible women reduced from 43.4% to 30.4% (95% CI 27.2–33.9). The hazard ratios increased to 4.34 (95% CI 3.52–5.35; p<0.001) comparing these ineligible women with trial control participants, and to 5.34 (95% CI 4.35–6.56; p<0.001) compared with trial SMS participants. When all 217 ineligible women without data were considered as all having received infant HIV testing, the cumulative probability of infant HIV testing among all trial ineligible women increased from 43.4% to 60.3% (95% CI 56.8–63.9). The hazard ratio comparing trial

control participants with ineligible women was lower but remained statistically significant (HR 1.68; 95% CI 1.40–2.02; p<0.001), as did the hazard ratio comparing trial SMS participants with ineligible women (HR 2.07; 95% CI 1.73–2.47; p<0.001). Results from sensitivity analyses did not change the interpretation of earlier results, confirming the robustness of our main findings.

2.1 Discussion

In this study, we found that undergoing recruitment, screening, and enrollment procedures for the TextIT randomized trial was significantly associated with improved rates of early infant HIV testing. Specifically, women enrolled in the trial control group were about three times more likely to have their infants tested for HIV compared to trial-ineligible participants. The effect of the SMS intervention was also much stronger when comparing women in the trial SMS group with women who screened but were not enrolled; being in the trial SMS group was associated with a four-fold higher rate of infant HIV testing compared to being ineligible for the trial.

Other studies have also found that participating in a randomized trial is associated with improved outcomes. For example, Baker et al. found that participants in trials to evaluate the effect of antidiuretic medication on cardiovascular outcomes, irrespective of trial group assignment, had significantly lower mortality than non-participants [78]. They defined this "clinical trial effect" as "a possible advantage for clinical trial participants over and above any effect of study medication [78]." Lascano et al. also reported a survival benefit among participants in clinical trials to evaluate medical therapies for bladder cancer compared to non-participants [79]. The "clinical trial effect" observed in our study was likely a result of a number of factors. These include additional interaction with health care workers, more intensive counseling during screening and consenting, more thorough service provision to women known to be in the trial, greater care in data collection and record completion, and the Hawthorne effect

– an awareness among participating women and non-study staff that they were being monitored. Importantly, LeVan et al. have shown that trial participation may lead to beneficial changes in clinical practice that last well beyond the trial period [80]. Other possible reasons for the "clinical trial effect" include trial eligibility criteria favoring women who were more likely to bring their infants for HIV testing, as well as poor record keeping for non-trial participants.

We identified a number of additional factors associated with completion of infant HIV testing by eight weeks postpartum. Increasing maternal age and education were both significantly associated with higher likelihood of undergoing infant HIV testing. These findings confirm those of Goggin et al. about the effect of higher levels of education on infant HIV testing in Kenya [81], and provide new insights about the effect of older age on timeliness of infant HIV testing. The association of increasing maternal age with timely infant HIV testing highlights the need to target younger mothers, including adolescents, with interventions aimed at increasing uptake of early infant HIV diagnosis services.

The most recent WHO recommendations for PMTCT include providing lifelong ART for pregnant and breastfeeding women living with HIV [18]. We were pleased to find that women receiving ART were more likely to have their infants tested for HIV compared to those not receiving ART. These results are consistent with those of other studies in Africa [21, 82, 83]. In contrast to women receiving ART, our results suggested that women who received components of the older WHO Option A prophylaxis regimen were much less likely to have their infants tested for HIV. These results highlight a potential additional benefit of hastening implementation of the current WHO guideline, which recommends initiation of lifelong ART for all pregnant and breastfeeding women living with HIV.

2.1.1 *Strengths and limitations – Data rich but information poor*

An important strength of this study was that our comparison group of women screened but not enrolled was contemporary with trial participants. This group also represented an important population that would be targeted by a facility-level implementation of this intervention in a real world setting. Comparing trial participants with non-participants is a means by which researchers can determine whether results from a randomized trial can be applied to the general population [84].

These results should be interpreted in the context of a number of limitations. First, we could not ascertain outcomes for approximately 30% of trial-ineligible women who did not have clinic records available. Excluding them might lead to selection bias. However, we conducted sensitivity analyses across the widest possible range of scenarios, and found that the interpretation of our main findings remained similar under both the most optimistic and most pessimistic assumptions. The problem of missing data in this analysis highlights one of the important challenges of using routinely collected data for research. The quality of data collected routinely for PMTCT and other HIV services is generally low compared to more rigorous data collection systems for research or surveillance [85-88]. Patient records may be incomplete, handwriting illegible, random pages torn, or entire registers missing. These data problems may be due to a number of factors including competing clinical tasks, staff shortages, logistical difficulties in timely supply of data collection tools, and the fact that routinely collected data are rarely used to inform ongoing patient care [89]. While these routinely collected records are a rich data source for patient, clinic, and country level evaluations, they must be interpreted in the context of substantial limitations. A second limitation was that the comparison between women enrolled in the trial and those screened but not enrolled was not randomized. Therefore, results

could have been influenced by unmeasured confounding factors. To maximize the validity of our results in the presence of residual confounding, we carefully constructed models that took into account known and potential confounders, including trial eligibility criteria. An analysis that included eligible but non-enrolled women might have resulted in a better comparison group for trial participants. However, this was limited by full participation of eligible women at participating facilities, and lack of data on eligibility among contemporaneous patients at non-participating facilities.

2.1.2 *Conclusion*

This study adds to a very limited literature in which investigators have compared outcomes between patients included and excluded from a randomized trial. Taken together with the findings of efficacy from the original randomized trial, the results of this analysis suggest that a broader rollout of the TextIT intervention could provide a substantial overall benefit. However, as Rothwell demonstrated in a seminal paper in the Lancet, "Routinely collected data … are an adjunct rather than an alternative" to randomized trials [90]. Therefore, we extended the findings from this analysis to explore the broader applicability of the TextIT intervention by designing a cluster-randomized, stepped wedge expansion. In this next step along the pathway from research to public health practice, we aimed to answer the broad question: is the intervention effective in real world routine care situations? The next two chapters describe the rationale, design, implementation, results, and conclusions of this expansion of the TextIT intervention.

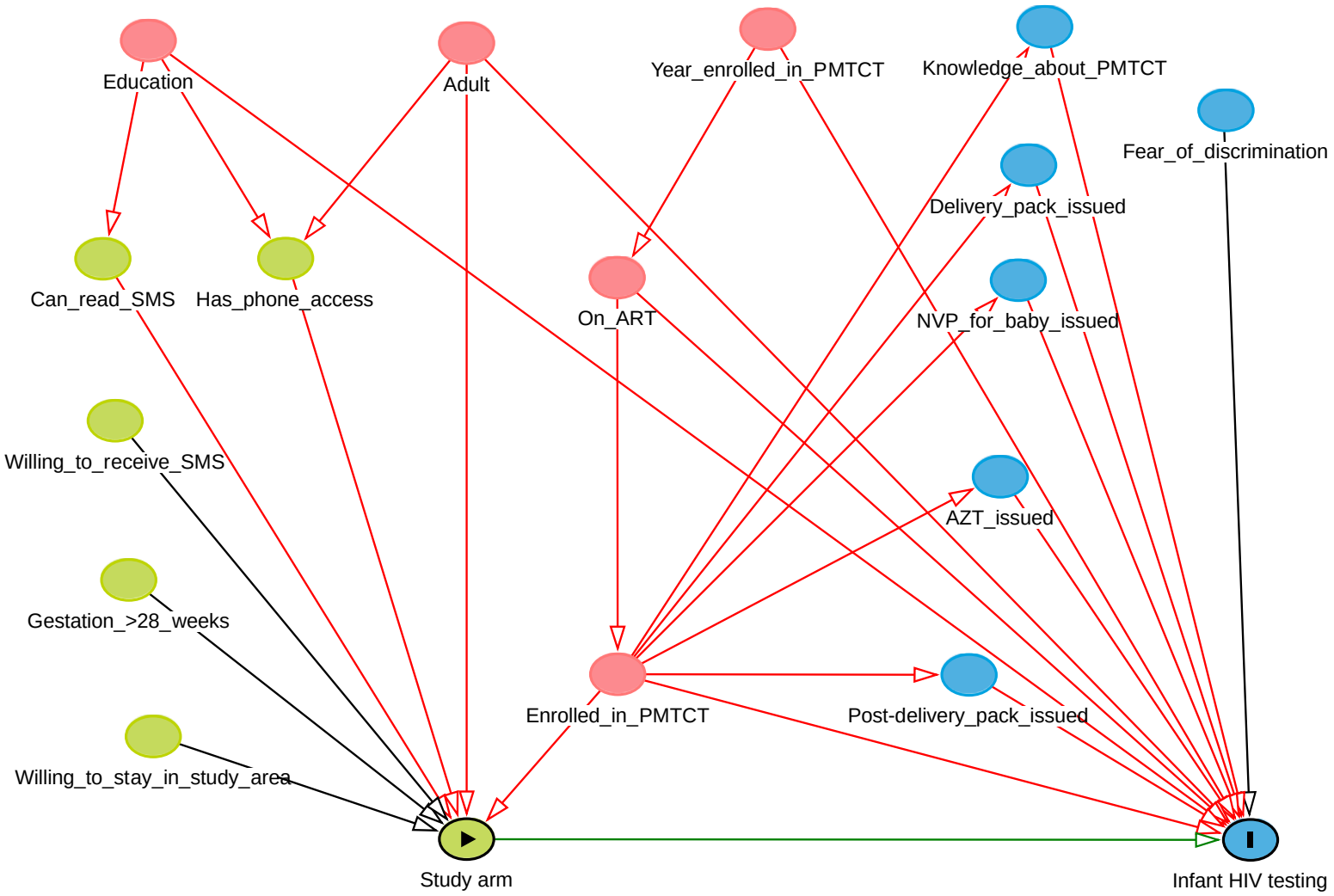

Figure 2.1. Directed acyclic graph showing relationships between factors known or suspected to be associated with trial participation (exposure) and infant HIV testing (outcome).

Key: green=ancestor of exposure; blue=ancestor of outcome; red=ancestor of both outcome and exposure

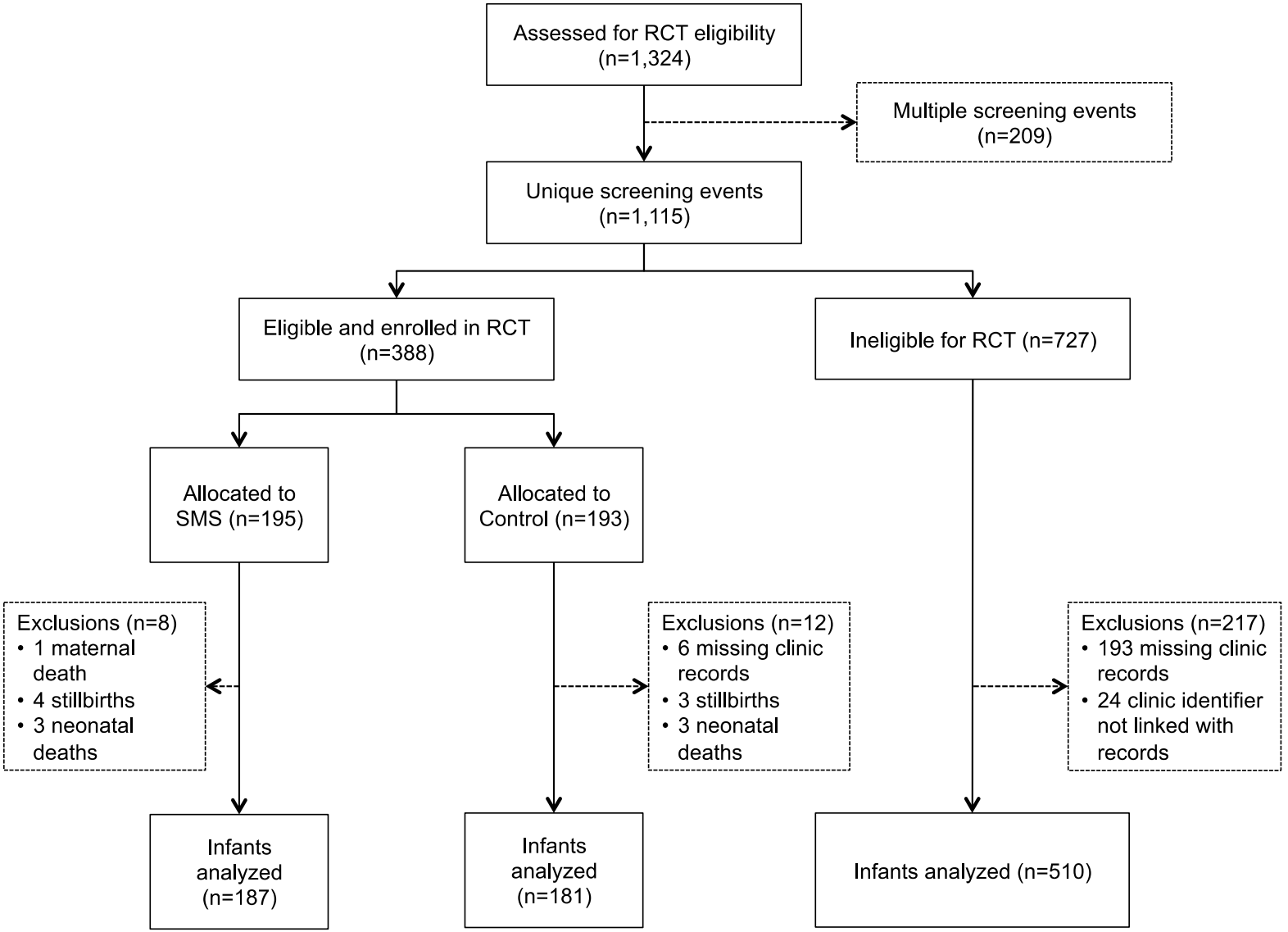

Figure 2.2. Study profile.

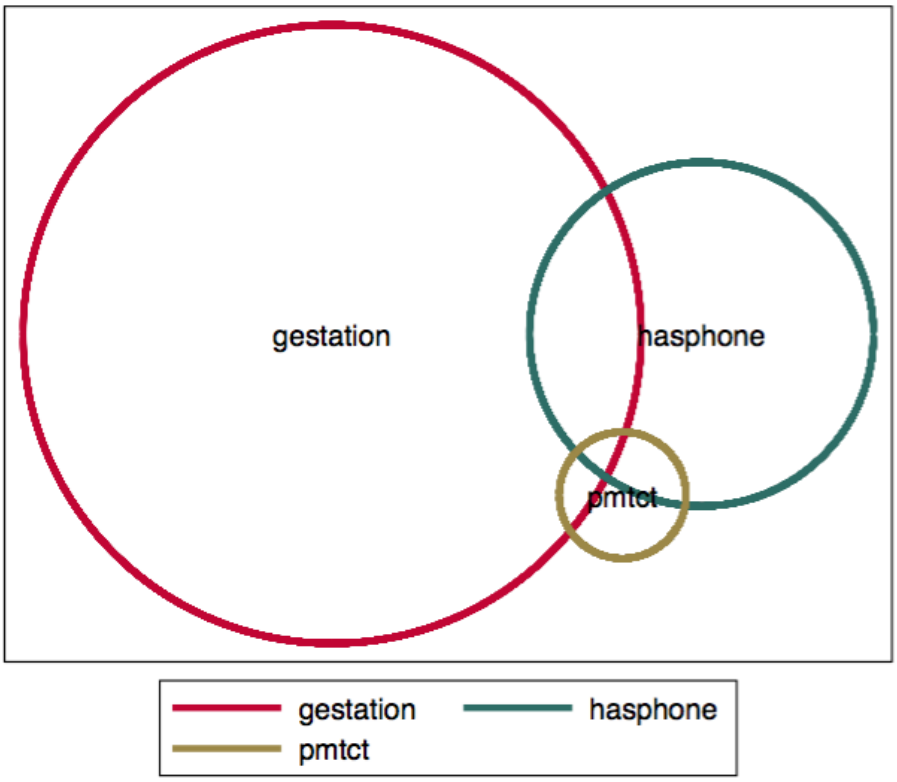

Figure 2.3. Venn diagram showing the distribution of trial exclusion criteria for adult women. gestation=women ineligible due to gestation <28 weeks (n=550); hasphone=women ineligible due to lack of phones (n=170); pmtct=women ineligible due to not being enrolled in the PMTCT program at the study clinic (n=23).

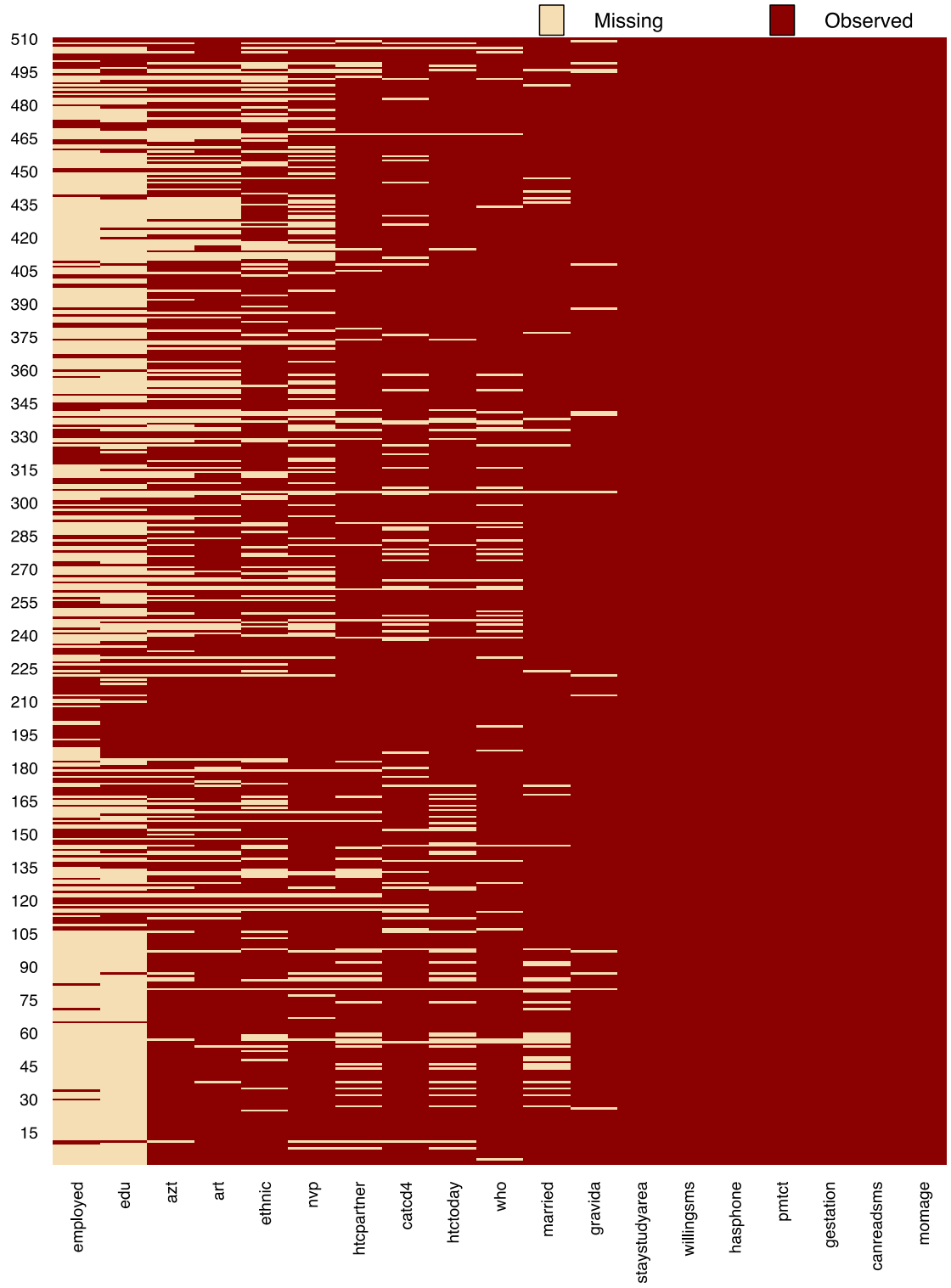

Figure 2.4. A "missingness map" showing patterns of missing data across baseline variables among trial-ineligible women. Each row on the vertical axis represents a participant; each column on the horizontal axis represents a variable.

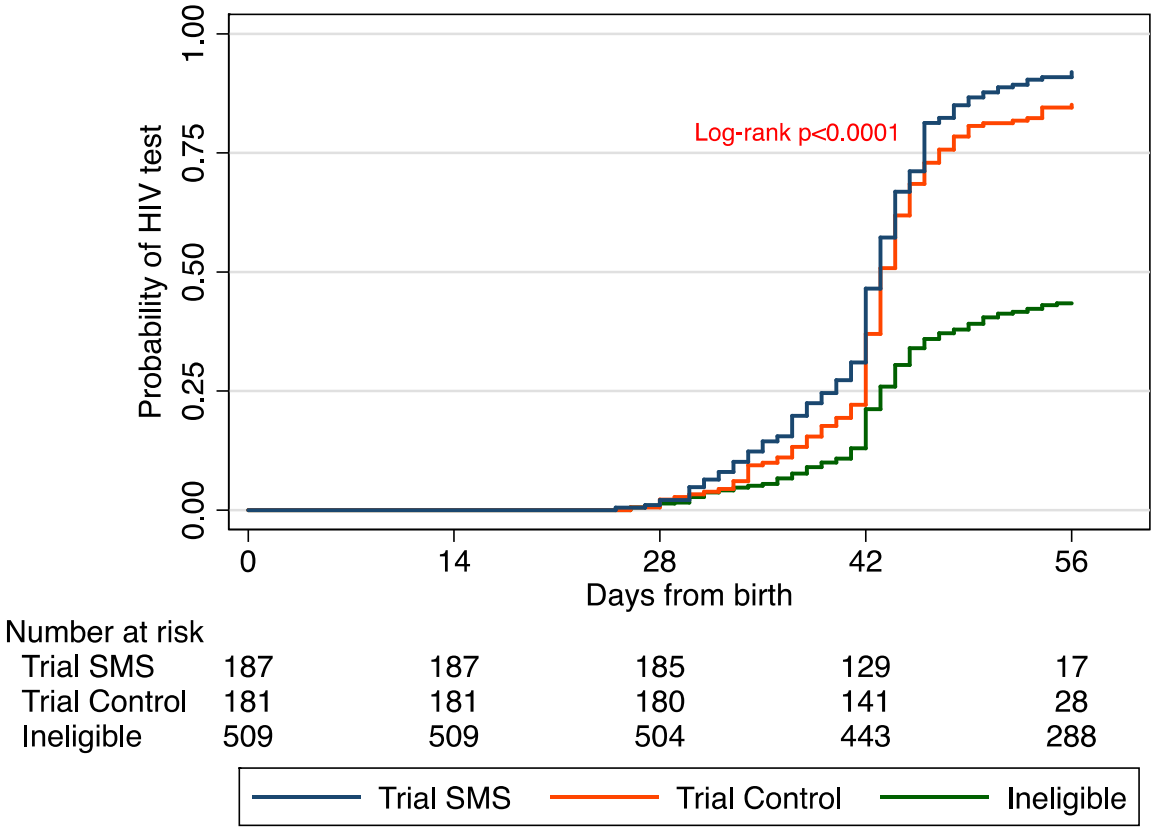

Figure 2.5. Kaplan-Meier plot showing time from birth to infant HIV virologic testing comparing trial participants in the SMS arm, trial participants in the control arm, and trial-ineligible participants.

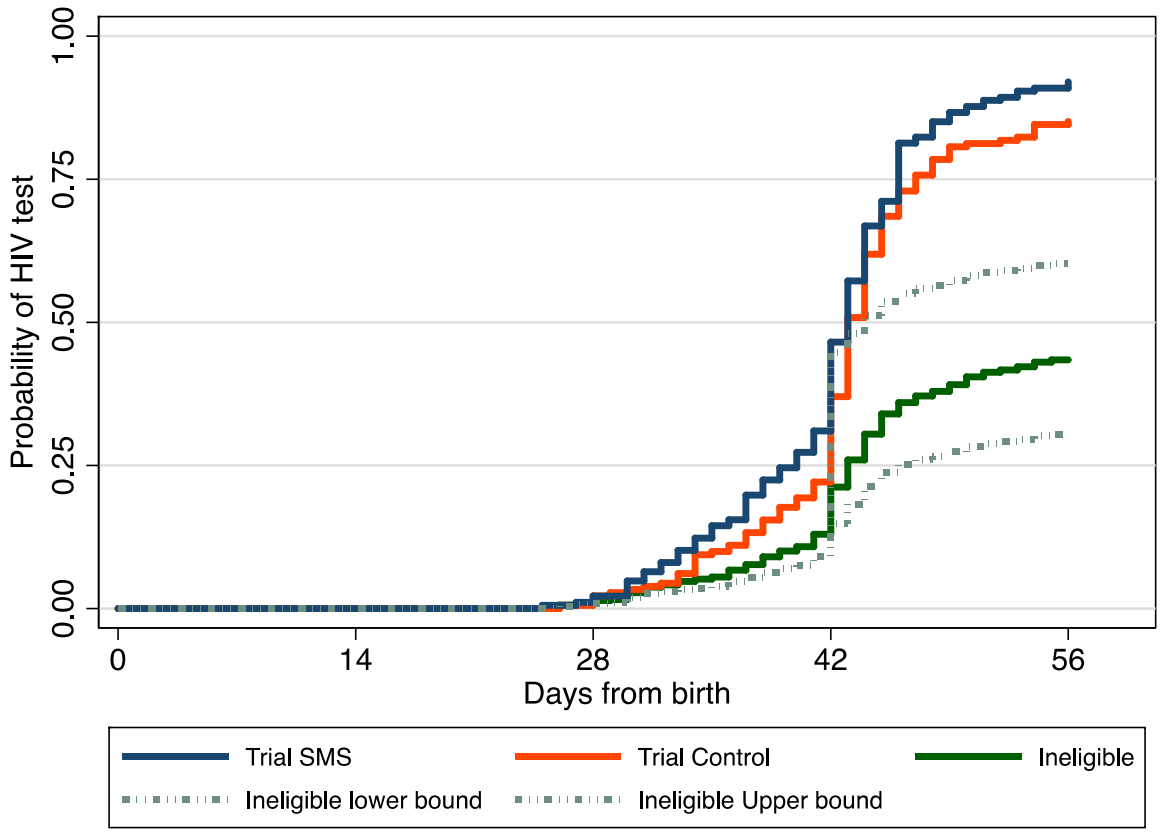

Figure 2.6. Sensitivity analysis showing Kaplan-Meier plot of time from birth to infant HIV virologic testing when all trial-ineligible women missing data are considered as either all failing or all receiving infant HIV testing or receiving.

Table 2.3. Trial eligibility criteria among women screened but not enrolled comparing those with clinic records available versus those without records.

	Available (N=510) N (%)	Not available (N=217) N (%)	Chi-square p-value
Adult 18 or older	503 (98.6)	211 (97.2)	0.20
Able to read SMS	505 (99)	217 (100)	0.14
Gestation >28 weeks	121 (23.7)	56 (25.8)	0.55
Enrolled in PMTCT program	497 (97.5)	207 (95.4)	0.15
Has access to mobile phone and if shared has disclosed HIV status	393 (77.1)	164 (75.6)	0.67
Willing to receive text messages	491 (96.3)	215 (99.1)	*0.04*
Planning to remain in study area during study	499 (97.8)	214 (98.6)	0.49

SMS=short message services; PMTCT=prevention of mother-to-child transmission of HIV

Table 2.4. Baseline demographic and clinical characteristics comparing trial participants versus those ineligible for trial participation

	Trial participants			
	Control (N=193) N (%)	SMS (N=195) N (%)	Ineligible (N=510) N (%)	Chi-square p-value
Maternal age (years)				
<18	0 (0)	0 (0)	9 (1.8)	0.08
18-24	65 (33.7)	60 (30.8)	188 (36.9)	
25-34	111 (57.5)	111 (56.9)	267 (52.4)	
35+	17 (8.8)	24 (12.3)	46 (9)	
Missing	0	0	0	
Education				
None	3 (1.6)	3 (1.5)	18 (3.5)	<0.01
Primary	110 (57)	115 (59)	119 (23.3)	
Secondary	55 (28.5)	64 (32.8)	26 (5.1)	
Post-secondary	25 (13)	13 (6.7)	13 (2.5)	
Missing	0	0	334 (65.5)	
WHO stage				
1	103 (53.4)	110 (56.4)	262 (51.4)	0.77
2	57 (29.5)	55 (28.2)	116 (22.7)	
3	27 (14)	23 (11.8)	74 (14.5)	
4	6 (3.1)	7 (3.6)	14 (2.7)	
Missing	0	0	44 (8.6)	
Most recent CD4 cell count				
<200	18 (9.3)	22 (11.3)	46 (9)	0.89
200-349	38 (19.7)	40 (20.5)	80 (15.7)	
350-500	55 (28.5)	54 (27.7)	119 (23.3)	
500+	82 (42.5)	78 (40)	206 (40.4)	
Missing	0	0	59 (11.6)	
Employed (vs. not employed)	39 (20.2)	35 (17.9)	36 (7.1)	0.64
Missing	0	0	346 (67.8)	
Luo ethnicity (vs. other)	177 (91.7)	188 (96.4)	384 (75.3)	0.01
Missing	0	0	115 (22.5)	
Married (vs. not married)	28 (14.5)	31 (15.9)	40 (7.8)	0.01
Missing	0	0	39 (7.6)	
First pregnancy (vs. >1)	29 (15)	27 (13.8)	92 (18)	0.25
Missing	0	0	15 (2.9)	
No previous deliveries (vs. ≥1)	29 (15)	27 (13.8)	93 (18.2)	0.22
Missing	0	0	15 (2.9)	
Receiving ART (vs. no ART)	102 (52.8)	101 (51.8)	221 (43.3)	0.42
Missing	1 (0.5)	0	123 (24.1)	

Received AZT prophylaxis	81 (42)	85 (43.6)	240 (47.1)	<0.01
Missing	1 (0.5)	0	154 (30.2)	
Received AZT+3TC+NVP (delivery pack)	53 (27.5)	60 (30.8)	237 (46.5)	<0.01
Missing	1 (0.5)	0	157 (30.8)	
Received AZT+3TC (post-delivery pack)	51 (26.4)	60 (30.8)	238 (46.7)	<0.01
Missing	1 (0.5)	0	157 (30.8)	
Prophylaxis for baby issued	133 (68.9)	139 (71.3)	384 (75.3)	<0.01
Missing	2 (1)	0	113 (22.2)	
HIV test done on screening day	5 (2.6)	5 (2.6)	87 (17.1)	<0.01
Missing	0	0	58 (11.4)	
HIV counseling with partner	49 (25.4)	40 (20.5)	147 (28.8)	<0.01
Missing	0	0	60 (11.8)	

ART=antiretroviral therapy

Table 2.5. Determinants of time to infant HIV virologic testing in Cox proportional hazards regression models.

Variable	Unadjusted		Adjusted *	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Exposure group*				
Ineligible	Ref.		Ref.	
Trial Control	2.85 (2.31–3.50)	*<0.001*	2.82 (2.29–3.48)	*<0.001*
Trial SMS	3.51 (2.87–4.30)	*<0.001*	3.48 (2.84–4.27)	*<0.001*
Eligibility criteria				
Enrolled in PMTCT program *	2.36 (0.88–6.32)	0.09	1.43 (0.53–3.84)	0.5
Adult 18 years or older	5.71 (0.80-40.62)	0.08		
Able to read SMS	1.87 (0.47–7.51)	0.38		
Gestation ≥28 weeks	2.29 (1.91–2.75)	*<0.001*		
Has access to mobile phone and if shared has disclosed HIV status	2.06 (1.54–2.80)	*<0.001*		
Willing to receive text messages	0.88 (0.51–1.53)	0.66		
Planning to remain in study area during study	0.78 (0.39–1.58)	0.50		
Baseline socio-demographic and clinical characteristics				
Maternal age (years)				
<18	Ref.			
18–24	3.38 (0.84–13.64)	*0.09*		
25–34	4.24 (1.06–17.04)	*0.04*		
35+	5.77 (1.41–23.56)	*0.02*		
Employed	1.11 (0.88–1.42)	0.38		
Education				
None	Ref.			
Primary	1.63 (0.95–2.80)	*0.07*		
Secondary	1.69 (0.97–2.96)	*0.06*		
Post-secondary	2.16 (1.19–3.94)	*0.01*		
Ethnicity (Luo vs. other)	1.51 (1.02–2.22	*0.04*		
Married (vs. not married)	0.80 (0.62–1.03)	0.08		
Second or higher pregnancy	1.10 (0.87–1.39)	0.82		
1+ previous deliveries	1.10 (0.87–1.38)	0.43		
WHO stage				
1	Ref.			
2	1.16 (0.95–1.41)	0.15		
3	1.26 (0.99–1.60)	0.06		
4	1.26 (0.80–1.98)	0.32		
Most recent CD4 cell count (cells/μL)				

<200	Ref.	
200–349	0.83 (0.60–1.14)	0.25
350–500	0.90 (0.67–1.21)	0.49
500+	0.86 (0.65–1.14)	0.31
HIV test day before date of screening	2.06 (1.49–2.85)	*<0.001*
HIV counseling with partner	1.19 (0.99–1.43)	*0.06*
Receiving ART for own health	1.44 (1.21–1.71)	*<0.001*
Received AZT prophylaxis during pregnancy	0.66 (0.56–0.79)	*<0.001*
Received AZT+3TC+NVP (delivery pack)	0.59 (0.49–0.70)	*<0.001*
Received AZT+3TC (post-delivery pack)	0.59 (0.49–0.70)	*<0.001*
Nevirapine prophylaxis for baby issued	0.67 (0.54–0.83)	*<0.001*

*The final multivariable model included exposure group and enrollment in PMTCT program. Both educational level and age were dropped from the multivariable model during the model building process, as neither variable meaningfully impacted the association between exposure group and HIV virologic testing of the infant.

Chapter 3. TEXT MESSAGING TO INCREASE RATES OF EARLY INFANT HIV TESTING

3.1 INTRODUCTION

Retention of children in PMTCT, including timely ART initiation, reduces mortality and limits morbidity associated with HIV. All children living with HIV should be initiated on ART [4], yet only 31% are currently receiving this life-saving treatment [3]. Left untreated, more than half of HIV-infected children will have died by two years of age [19]. Timely diagnosis of HIV infection among infants is the *sine qua non* of successful ART initiation, yet only 49% of HIV-exposed infants were tested in 2014 [3]. The new "90-90-90" global initiative led by the Joint United Nations Programme on HIV/AIDS (UNAIDS) targets testing 90% of all people living with HIV, treating 90% of all who test positive, and achieving viral suppression among 90% of all those receiving treatment by 2020 [91]. Improving early diagnosis of infant HIV infection is essential for improving the lives of children and achieving these targets.

We designed the TextIT strategy, a theory-based text messaging intervention, to increase uptake of infant HIV testing by leveraging the rapid rise in mobile phone connections in Kenya. Mobile health (mHealth) technologies are appealing as a bridge to achieving higher rates of infant HIV testing for a number of reasons. These include their widespread use among health workers and patients, low cost, and inherent flexibility for adaptation that is rarely seen with other interventions [37]. In a randomized controlled trial, we found the TextIT intervention to be efficacious for improving infant HIV testing rates [39]. Evidence of effectiveness under real-world routine care conditions will likely be necessary to achieve policy change leading to broader implementation. Policy makers, in general, are reluctant to adopt efficacious

interventions that lack evidence of effectiveness. To address this gap, we expanded TextIT using an implementation science approach [43], with the goal of generating evidence of effectiveness for increasing rates of early infant diagnosis (EID) of HIV outside of a controlled research setting.

3.2 METHODS

3.2.1 *Study design*

The TextIT study was a pragmatic, cluster randomized, stepped-wedge trial with two time periods of observation. Twenty clusters were selected for implementation. Ten clusters were randomly allocated to begin implementing the intervention immediately, while the remaining 10 began implementing approximately six months later. Figure 3.1 shows the stepped-wedge design of the TextIT study.

3.2.2 *Rationale for a cluster-randomized stepped wedge design*

We chose the cluster as the most appropriate unit of randomization because under routine care settings, public health interventions are implemented at the health facility level. This design also allowed us to capture the effects of the intervention on the health system [92], and maximized the potential for producing generalizable findings. As we had previously shown that this intervention is efficacious, equipoise was not justifiable within the same setting–this intervention would likely do more good than harm. However, due to logistical, financial, and human resource constraints, it was not feasible to expand the intervention to all facilities at the same time. The stepped wedge design addressed ethical concerns by ensuring that no targeted health facility was deprived of an efficacious and potentially effective intervention. This design also reduced the

risk of “contamination” of the intervention effect. In an individually randomized design, women who are allocated to receive text messages could potentially share the messages with those allocated to the control arm at the same health facility. Additionally, staff members who are aware of on-going observation might make extra effort to counsel women and improve follow-up and record keeping (the Hawthorne effect) [93]. Both the individual-level and facility-level effects could modify behaviour among control group women, resulting in contamination. The selected health facilities were run by the Ministry of Health. By design, these facilities were geographically spread out, so that they would be likely to capture distinct catchment areas. This reduced the likelihood of the intervention effect “spilling over” to control facilities due to interaction between women attending care at different clinics. As a result, randomization at the cluster level was intended to enhance internal validity by avoiding contamination at the individual level, minimizing a potential reduction in the effect size.

3.2.3 *Participants*

Study clusters were defined as health facilities supported by the Family AIDS Care and Educational Services (FACES) to provide PMTCT services. FACES is a PEPFAR/CDC funded HIV prevention, care and treatment program operated jointly by the Kenya Medical Research Institute (KEMRI) and the University of California, San Francisco. FACES cares for over 80,000 patients and supports 136 government health facilities, spread across three counties (Kisumu, Migori, and Homa Bay) in the Nyanza region of Kenya. This region has the highest HIV prevalence in the country (15%) [94]. Distribution of selected health facilities across the three counties is shown in Figure 3.2.

Potential participants included all HIV-positive pregnant women enrolled in the PMTCT program at target health facilities. Because this study was designed as a pragmatic trial to

estimate effectiveness of TextIT under real world conditions, inclusion criteria were minimal. Women were offered the opportunity to receive text messages if they were ≥18 years or emancipated minors, and between 28 weeks gestation and delivery. Similar criteria were used to abstract data for women at control facilities. Women in the intervention group who reported sharing phones were excluded if they had not disclosed their HIV status to the person sharing the phone.

3.2.4 *Randomization*

An independent biostatistician at the University of Washington's Center for AIDS Research Biometrics Core generated the randomization sequence for each stratum and assigned clusters to the different intervention start periods. The biostatistician was not involved in any other aspects of the study. Randomization was stratified by clinic volume and experience level. Clinic volume was measured by the average number of pregnant women newly enrolled into the PMTCT program in the 12 months prior to randomization (≥50 versus <50 enrollments per month). Facilities were considered to have prior experience with TextIT if they had been part of a 6-month pilot project run by FACES immediately after release of the initial trial's results [39]. Stratification was implemented by dividing the 20 clinics into 4 strata such that clinics within each stratum had similar volume and experience. There were a total of 2, 6, 6, and 6 clinics in strata 1, 2, 3, and 4 respectively. Randomization was conducted separately within each stratum. Each clinic was assigned a random number. Clinics with low random number values (defined as less than the stratum median value) were assigned to start intervention immediately, while clinics with high random number values (greater than stratum median) were assigned to start intervention six months later. Due of the nature of the intervention and the need to inform facilities of their participation, it was not possible to blind clusters, health care providers,

investigators, or individual participants to the group assignments. Health workers at control facilities were aware of the study and outcomes being evaluated, and that data were being abstracted from clinic records, but continued to provide usual care.

3.2.5 *Training of implementers at intervention health facilities*

"Mentor mothers" at each health facility abstracted data from routine clinic records and registered women to receive text messages at intervention facilities. Mentor mothers are a formal lay cadre of women living with HIV who have recent experience in PMTCT (6 months to 2 years). They are deployed to maternal and child health clinics (MCH) to share best practices of PMTCT with their peers attending care, and are employed by health facility management boards or organizations supporting HIV care at a health facility (such as FACES) as part of the Ministry of Health-approved Kenya Mentor Mother Program [95]. Other health facility staff at the MCH reviewed patients, dispensed medication, provided counseling, obtained dried blood spot samples from HIV-exposed infants, and filled registers as part of their routine work. Phase one intervention sites were trained immediately after randomization, while phase two intervention sites were trained at the end of their control period, immediately prior to implementing the intervention. Training on the TextIT strategy targeted all service providers at the MCH, but mentor mothers played the leading role in implementation. Training was done by a team comprising the study principal investigator, study coordinator, study nurse, and the head of the FACES PMTCT program. Training was conducted in two stages. The first was a two-day, conference-based training at a central location attended only by mentor mothers. The second was a one-day, facility based training for all MCH service providers at each health facility. The two-day training for mentor mothers included didactic and practical sessions on each day. Didactic sessions on the first day included a review of PMTCT services and national guidelines, overview

of the study protocol, data collection instruments, and training on research ethics. Practical sessions included role-plays on recruitment and enrolment procedures, a familiarization tour of the PMTCT services at two large health facilities, and group discussions on the day's experiences. The second day included didactic sessions on data collection using a mobile phone-based system, and how to register patients to receive SMS from the automated text messaging software. Practical sessions included role-plays on data abstraction from routine registers, and registration into the SMS system. At the end of the two-day training, an evaluation of competence was conducted. Each mentor mother was required to obtain certification of ethics training by taking an online course following the two-day training. The second stage of training was completed onsite at each health facility. During the second phase, all MCH service providers were given an overview of the TextIT implementation protocol, data collection procedures, SMS-based participant registration, and the role of the mentor mother in implementing TextIT. This second phase also allowed trainers to meet mentor mothers and address gaps in competency that may have been identified by the evaluation that followed the initial two-day training.

3.2.6 *Interventions and study procedures*

At facilities randomized to continue usual care, women did not receive any study-related intervention. Mentor mothers at these facilities were trained in person at their respective facilities on abstracting data from health facility records as part of routine program evaluation. Because they were paid by funds from the TextIT study, they were aware of the general nature of the intervention and outcome being measured, but did not receive any other training until the end of the control period, immediately prior to implementing the intervention. When health facilities implemented TextIT, both in phase one and phase two of the study, mentor mothers were trained to provide a brief overview of the TextIT strategy, obtain verbal consent to receive the

intervention, and provide a written information statement to women willing to receive messages. As with other interventions offered as part of standard care, women could ask questions, and health facility staff were on hand to respond. Baseline clinical and demographic characteristics were recorded only for women who provided informed consent, after which they were registered to receive intervention text messages. Participants were registered by sending a text message in a pre-defined format that included the participant's study identification number, date of the last normal menstrual period, and preferred time of day and language for receiving messages. Languages available included English, Kiswahili, and Luo. Women also had the option of providing a preferred name to be included in outgoing text messages. Women attending clinics implementing TextIT who lacked phones continued to receive standard care. However, they were considered as having been exposed to the TextIT intervention in the intent-to-treat analysis.

Registered women received up to 14 text messages during pregnancy and after delivery. Messages were sent on weeks 28, 30, 32, 34, 36, 38, 39, and 40 during the third trimester of pregnancy. One message per week was sent for the first six weeks after delivery. The message content and schedule were the same as those used in the earlier study that determined the efficacy of this intervention (Table 3.6) [39]. Participants at facilities implementing TextIT had the option to respond to text messages, call, or send inquiry text messages to a designated clinic phone. One nurse was designated to respond to all calls and text messages. Participants could also request a call from the nurse by sending a free "call back" text message to the designated clinic phone at any time. If a participant requested to be called back, our automated software acknowledged the request by sending back a message in the participant's preferred language containing the text, "Thank you. A nurse will call you soon." At the same time, the software sent a message to the nurse containing the text, "Patient [name] has asked to be called at [phone

number].” Upon receiving this message, the nurse called the participant and recorded details of the conversation on a standardized clinic form. An experienced clinical provider from the FACES program was available for consultation by the TextIT nurse at any time through the *Uliza!* consultation service [96]. *Uliza!* is a toll-free 24-hour telephone consultation service for HIV clinical service providers in Kenya that is run by FACES in partnership with the National AIDS and STI Control Program.

Beginning in the 37th week of gestation, mentor mothers reviewed clinic records daily to determine whether delivery had occurred at the health facility. If delivery had not occurred at the facility, the TextIT nurse called text message recipients weekly, beginning at 37 weeks, to determine whether they had delivered elsewhere. If delivery was confirmed, the nurse recorded the date, outcome, place, and mode of delivery. Additionally, the baby’s sex and name were ascertained, and this information was used to update subsequent automated text messages. Where delivery had not occurred, participants were called again a week later and every week thereafter until delivery status was ascertained. In practice, most participants either sent a text message or called to report delivery. To ascertain delivery status for participants at control facilities, mentor mothers reviewed clinic records daily, beginning from the estimated date of delivery. For all participants, if no record of delivery existed at the facility at the end of the follow-up period, clinic staff obtained this information at the first postnatal contact with the mother (for women who visited the clinic). Participants at intervention facilities were offered the option to stop receiving text messages by presenting to the clinic and indicating their desire to stop, or by sending an SMS with the word ‘STOP’, although none did.

3.2.7 *Outcomes*

Women were routinely asked to bring their infants for HIV testing at 6 weeks postpartum (to coincide with the routine immunization clinic visit). Our primary outcome measure was infant HIV virologic testing, defined as obtaining a dried blood spot sample for HIV polymerase chain reaction (PCR) testing within eight weeks after birth. Using the same procedure as our earlier efficacy study [39], we assessed infant HIV testing by abstracting information from medical records, including the HIV exposed infant (HEI) follow-up register, HEI card, and laboratory registers. At FACES, routine care included intensive tracing efforts for women who failed to attend clinic appointments, to ascertain reasons for appointment default and to engage them back in care. We relied on this well-established tracing program to ascertain birth and other outcomes for women who failed to return to clinic [97, 98]. Women who could not be contacted were considered to have failed to obtain HIV testing for their infants. Women who voluntarily transferred out to facilities not supported by FACES were excluded from analysis, as we had no mechanism to trace them outside the FACES network. For multiple infant pregnancies our analysis was restricted to the firstborn infant. Infants of women who died during follow-up, stillbirths (fetal loss after 28 weeks of pregnancy), and infant deaths before eight weeks were excluded from the analysis.

As a secondary outcome, we assessed the time to infant HIV testing using Kaplan-Meier plots, a log-rank test, and Cox regression analysis with clustered robust standard errors. Time to infant HIV testing was measured in days from the date of birth to the date when a dried blood spot sample was obtained for HIV testing. Survival time was censored after 8 weeks following delivery (56 days) or at the time of infant deaths occurring before 8 weeks.

3.2.8 *Power and sample size determination*

The primary outcome, completion of early infant diagnosis (EID) of HIV within eight weeks of delivery, was binary, and measured at the individual level. We estimated a relative risk comparing the proportion of infants who were tested for HIV in the intervention period compared to the control period. For a stepped-wedge design with *I* clusters, *T* time points, and *N* individuals sampled per cluster per time interval, let Y_{ijk} be the value of the outcome (0 or 1) in infant *k* at time *j* from cluster *i* (*i in 1, …, I; j in 1, …, T; k in 1,…, N*). Let X_{ij} be an indicator of the treatment assignment in cluster *i* at time *j*, with 0=control and 1=intervention. The primary measure of treatment effect is a log relative risk denoted θ; the estimate of the treatment effect is $\hat{\theta}$. We used the method described by Hussey and Hughes [99] to determine power to test the hypothesis $H_0: \theta = 0$ versus $H_A: \theta \neq 0$ for the primary outcome. We designed a study with *I* = 20, *T* = 2, mean *N* = 57, and sample size of 2,280. We assumed a coefficient of variation between clusters (τ/μ) of 0.25 and calculated the power for a two-tailed test with α=0.05. Assuming that 40% of infants in the control group would undergo HIV virologic testing, we estimated having ≥90% power to detect an increase to 53% or greater in the intervention group. Presuming 10% loss to follow-up, we proposed a final sample size of 2,508 women.

3.2.9 *Statistical analysis*

All analyses were performed using Stata software (StataCorp, College Station, TX). We described participant characteristics at baseline in control and intervention groups. Inferential analysis for the primary outcome followed the intent-to-treat principle. All participants were analyzed according to the cluster randomization group at the time of enrollment. Participants at facilities implementing the TextIT intervention were all considered to be in the intervention

group, regardless of whether they received the intervention or not. Our primary analysis was on the individual-level binary response values, Y_{ijk}. The predictor of interest was treatment assignment (cluster-level values X_{ij}). Time period j was included as a covariate. A covariate for the stratum of randomization was also included [100]. Our analysis used generalized estimating equations (GEE) methods on the individual-level data to account for variable cluster sizes. Such methods are robust to misspecification of the variance structure when the "sandwich" estimate of the variance is used [99]. Specifically, we used modified Poisson regression with robust variance estimation to estimate the relative risk and 95% confidence intervals (CIs), using GEE with working exchangeable correlation structure to account for clustering by site [101]. All tests were two-sided and conducted at the 5% significance level.

3.2.10 *Ethical considerations*

County health officials provided written permission for the health facilities in their respective jurisdictions to take part in the study. All text message recipients provided verbal informed consent to receive the messages. Upon the release of our initial randomized trial findings, FACES conducted a pilot of this intervention at six facilities for six months to determine feasibility for inclusion as part of the standard package of care. Following the pilot, FACES included the intervention as part of routine care for pregnant and postpartum women living with HIV attending care at the six health facilities where the pilot took place. However, funding constraints led to cessation of this activity in July 2014 (approximately six months prior to this TextIT expansion). Directors of the health departments in the target counties of Kisumu, Homa Bay, and Migori supported the expansion of TextIT as part of standard care. In this context, the usual practice at Ministry of Health facilities is to obtain verbal consent. As such, although this intervention was at the health facility level, we sought individual patient verbal consent for all

women receiving text messages. For women at health facilities not implementing the TextIT intervention, we were not required by the institutional review boards (IRBs) to obtain individual-level consent to collect outcome data. As part of the FACES program, we had continuing approval from the relevant IRBs to collect such data that were already being captured routinely for evaluation without obtaining individual-level consent. Ethical approval was obtained from the Kenya Medical Research Institute's Scientific and Ethics Review Unit, the University of Washington's Human Subjects Division, and UCSF's Committee on Human Research. The trial is registered in ClinicalTrials.gov (#NCT02350140).

3.3 RESULTS

3.3.1 *Study participants*

The flow of clusters and participants through the study is reported using a diagram (Figure 3.3) modified for a stepped wedge design from the suggested "CONSORT" format for cluster randomized trials [102]. We assessed patient volumes at all 136 health facilities supported by FACES to offer PMTCT services, and included the top 20 in the study. Database closure for this analysis was May 20, 2016. All participants who had completed follow-up by this date were included in the present analysis. Between February 11, 2015 and May 20, 2016, 3,830 women were assessed for study participation at the 20 health facilities (5,225 screening visits in total). Of these, 1,894 who were less than 28 weeks pregnant were excluded. In the intervention phase, we excluded 35 who declined participation and one who shared a phone but had not disclosed to the person sharing. Overall, 1900 women participated in the study, including 751 at step 1 control facilities, 599 at step 1 intervention facilities, and 550 in step 2 across all 20 facilities. Table 3.7 shows the baseline characteristics of women by intervention and control groups. Maternal demographic and clinical characteristics at enrollment were well balanced across both

groups. Overall, the median age at enrollment was 27 years (interquartile range [IQR] 23–30), and only 36 (2%) of enrolled women were less than 18 years old. The median gestational age at enrollment was 30 weeks (IQR 28–34). The majority of women were unemployed (1,419/1,900; 75%), had completed primary education (1,257/1,900; 66%), and were married (1,723/1,900; 91%). The median CD4 cell count at enrollment was 477 cells/μL (IQR 328–670), and 13% were classified as WHO stage 3 or 4. Nearly all women (1,895/1,900; >99%) were receiving ART as part of the Option B+ program (lifelong ART for all pregnant and breastfeeding women living with HIV), and a high proportion (1,784/1,900; 94%) had been tested for HIV before the study enrollment day. There were 1,637 (86%) of 1,900 women who owned a phone. Of these, 416 (25%) reported sharing their phone and had disclosed their HIV status to the person sharing.

Of the 1,900 women enrolled, we excluded 8 who died (5 before and 3 after delivery), and 15 who transferred to other health facilities not supported by FACES (12 before delivery and 3 after delivery). Among the remaining 1,877 women, 81 were lost to follow-up and 1,796 were known to have delivered. Of these, 1,746 (97%) were live births (singleton or first baby for multiple pregnancies) and 50 were stillbirths. There were 38 infant deaths before eight weeks, leaving 1,708 infants who survived to eight weeks. The primary analysis included 1,789 infants. Of this group, 1,708 were live births that survived to eight weeks and 81 were lost to follow-up, and therefore considered to have failed to complete HIV testing prior to eight weeks of life. Table 3.8 shows infant characteristics at birth.

3.3.2 *Infant HIV testing*

Of the 1,789 infants analyzed, 1,551 (87%) had HIV virologic tests performed before eight weeks. Of these, 951 of 1,076 (88%) were in the intervention group and 600 of 713 (84%) were in the control group (relative risk [RR] 1.05; 95% CI 0.98–1.12; p=0.2). Kaplan-Meier estimates

of the cumulative probability of infant HIV testing did not differ comparing the SMS group to the control group (log-rank p=0.5; Figure 3.4).

3.4 DISCUSSION

In this cluster randomized, stepped-wedge trial of a theory-based text messaging intervention to improve uptake of infant HIV testing under routine care conditions, we found that a greater proportion of infants of women in the intervention group received HIV testing compared with the standard care group, but the difference was small, and not statistically significant. This finding was likely influenced by a surprisingly high rate of early infant HIV testing even during the control period in facilities that did not receive the intervention during the first phase of the trial.

These results should be interpreted in the context of both the earlier successful efficacy trial [39], and a follow-up analysis that explored outcomes in women screened but excluded from that study (Chapter 2). We achieved 92% testing among intervention group participants in the efficacy trial. It is encouraging that the proportion of infants tested in the present effectiveness study was nearly as high at 88%, especially given that 12% of women in the intervention group did not have phone access and therefore could not actually receive text messages. In the efficacy trial, women without access to phones were ineligible for participation.

In the present study, we observed a high HIV testing proportion among infants in the control group (84%). This finding is similar to the 85% observed in the control arm of the earlier efficacy trial. However, it is a surprising departure from the background testing rates observed within the FACES program around the same time as the effectiveness study (68% between October 2014 and September 2015) (J. Kulzer, personal communication, July 4, 2016). The high proportion of early infant HIV testing observed among control group participants in the TextIT expansion could be due to a number of reasons. First, “contamination” of usual care procedures

could have occurred in control facilities. Health workers at control facilities were aware of ongoing monitoring for the trial, including evaluation of rates of EID completion, and could have made the extra effort to counsel women about the importance of infant HIV testing. Facility staff might also have taken additional measures to follow up women in the PMTCT program because of their knowledge of the monitoring. This situation would be analogous to the "trial effect" we observed in the efficacy trial and analyzed in Chapter 2 of this dissertation. Second, there were multiple concerted efforts by programs in Kenya, and FACES in particular, aimed at increasing EID to meet the deadline for eliminating mother-to-child HIV transmission by 2015 [103]. Many of these interventions were implemented around the same time as the TextIT expansion. For example, the FACES program scaled up integration of PMTCT services in antenatal clinics to improve uptake of services along the PMTCT cascade. This scale-up was informed by the results of a study within the same program, which showed a non-significant statistical trend towards improved EID with service integration [104]. In addition, FACES modified defaulter management procedures by including phone calls to women who missed clinic appointments. This was aimed at improving retention in PMTCT, including EID. At the same time, a new initiative was launched to have shorter intervals between appointments for women attending PMTCT, as opposed to the minimum one-month interval implemented previously. Finally, introduction of the Kenya Mentor Mother Program nationally beginning in November 2012, with the aim of achieving 80% EID by 2015, could also have contributed to improvements in EID [95].

A careful search of the literature suggests that our TextIT strategy may be the first mHealth intervention to be evaluated in both an efficacy trial and a real-world implementation setting. The mHealth field is replete with pilot interventions, some with evidence of efficacy, but

deficient in uptake and translation of interventions for public health impact [38, 105]. In a recent article (April 2016), Yasmin and colleagues reviewed mHealth interventions for chronic disease care and concluded that none met the standards sufficient for scale-up [106]. This was similar to the conclusion reached by Tomlinson and colleagues three years prior [38]. The Society for Prevention Research has developed standards to determine the readiness of interventions for scale-up [107]. These standards include efficacy trials under ideal conditions, subsequent effectiveness trials under real-life conditions, and dissemination research to ensure that the intervention can be implemented with fidelity to the original design. As evidence of efficacy, our initial randomized trial enabled the establishment of a causal effect between text messaging and higher rates of infant HIV testing. We then evaluated the TextIT intervention for effectiveness under real-world conditions. To ensure fidelity of the intervention, this strategy included the same message content, messaging schedule, and automated registration into the SMS system as in the efficacy trial. To further prepare for broader dissemination, we developed a text messaging protocol, training manuals, implementation procedures and checklists, data abstraction forms, lists of frequently asked questions, and the automated text messaging software. However, the lack of a large and statistically significant effect of the intervention in this effectiveness trial raises important questions about broader expansion. The analysis for completion of this dissertation was conducted after accruing 75% of participants towards the target sample size. The complete (and definitive) analysis will have somewhat greater statistical power. Nonetheless, it is clear that the magnitude of the effect of the intervention compared to the control condition will be small.

Our implementation science approach to improving EID had a number of strengths. First, we used a cluster-randomized design to enable strong causal inference. Second, to further

demonstrate effectiveness, we used a pragmatic trial design, with minimal inclusion criteria. This broadened the study population at intervention facilities to be more representative of the entire target population (pregnant women living with HIV), and enhanced the generalizability of the TextIT strategy. For example, our analysis included women who lacked access to phones, although this meant that they were unable to receive text messages. We also included pregnant adolescents living with HIV, a group typically neglected in PMTCT research [108, 109], and excluded from our earlier efficacy trial. Third, we used regular personnel at health facilities (mentor mothers), rather than research staff, to deliver the intervention. These health workers incorporated study-specific procedures into their routine daily tasks. Finally, we abstracted data from routine records, and did not provide staff or patient incentives for study participation. These approaches ensured that implementation approximated routine care conditions.

Our study had a number of limitations. Awareness of ongoing observation and evaluation of EID completion rates at control facilities could have resulted in contamination at these facilities. In addition, some facilities in the control condition had been part of a pilot implementation of the intervention that occurred prior to the effectiveness study. To address this limitation, we stratified randomization by experience in the pilot, and adjusted for stratification in the analytical model. Another limitation was that our study was conducted in a high HIV prevalence area. This could reduce the generalizability of our findings to areas with low HIV prevalence. Finally, our approach failed to identify that simple improvements in delivery could increase EID rates substantially, even before considering a technological solution. As suggested by our Chapter 2 analysis, the high testing rates in the control groups of both the efficacy and effectiveness trials were likely due to a high standard of delivery of usual care, including diligent documentation of follow-up, improved data quality, a respectful attitude toward women

attending clinic, and one-on-one counseling. In formative theory-based qualitative studies, we asked women and health workers about potential barriers to infant HIV testing and how text messages could help them overcome these barriers [40]. While this approach to addressing an implementation science question was pivotal in understanding the gap and guiding the development of the TextIT intervention [110], it assumed that these barriers could be addressed using text messages.

Despite the lack of a significant effect of the intervention on EID rates in this study, key lessons have emerged, both for strengthening efforts to eliminate mother-to-child HIV transmission and for implementation research more generally. Perhaps most important, improving the implementation of usual care was sufficient to substantially improve infant HIV testing rates. The "rapid results initiatives" within the FACES program are an excellent illustration of this point. In the context of these initiatives, simple strengthening of existing health systems intensively over a short period increased EID from 46% to 87%, although the effects were short-lived [67]. Another example comes from a study in Cote d'Ivoire, Kenya, and Mozambique, which found that using a "systems analysis approach," where facilities iteratively identified and resolved barriers to PMTCT service delivery, led to a 17-fold increase in infant HIV testing [111]. Our earlier efficacy study showed that under ideal conditions, text messages could have a benefit even beyond good service delivery. In contrast, the present study showed that in a real-world setting, most of the benefit was probably from the basic improvements created by monitoring, rather than from text messaging. This intervention could potentially have higher impact if implemented in regions with low rates of infant HIV testing. In Chapter 2, we found that when background testing rates were low, women who received SMS were more than three times more likely to have their infants tested for HIV compared to those receiving usual

care. However, in settings with low EID rates, it remains unclear whether simple system improvements could be enough to attain high testing rates, or whether such improvements should be paired with SMS. Our effectiveness study showed that even with high background testing rates, neither system improvements alone (control) nor system improvements with SMS (intervention) achieved the UNAIDS target of 90% testing. Could pairing of system improvements with SMS in low EID settings (as in the efficacy trial) achieve the target of 90% testing under real-world low EID conditions? A similar effectiveness study should be conducted in low EID settings to answer this question more directly.

3.4.1 *Conclusion*

There has been great progress globally in development of interventions to support PMTCT toward the goal of elimination of mother-to-child HIV transmission (eMTCT). The survival of HIV-exposed infants, and the ultimate goal of achieving an AIDS-free generation, will depend on successful translation of these evidence-based interventions into routine and sustained public health programs [112]. We have previously shown that theory-based text messages are efficacious for improving rates of early infant HIV diagnosis, the most crucial entry point into care for HIV-exposed infants, and a core component of PMTCT [39]. In the present effectiveness study, high testing rates were achieved in the control arm. This could have been a result of contamination of the control arm by improving basic services, improvements across the region due to efforts to meet the 2015 eMTCT goal, or both. Our present findings suggest one of two conclusions. The intervention could have been overtaken by events in the current environment of high EID rates within the large FACES program; or the unavoidable effect of contamination in the control arm due to monitoring precludes the observation of statistically significant differences. Yet, EID rates still fall short of the 90% UNAIDS target towards 90-90-90. Getting

"over the hump" to reach at least 90% infant HIV testing calls for more implementation research to better understand the gap, and to develop context-sensitive interventions to bridge the gap. A more comprehensive approach might result in a menu of interventions tailored to specific environments, targeted at a variety of health system components, and attuned to diverse EID prevalence rates.

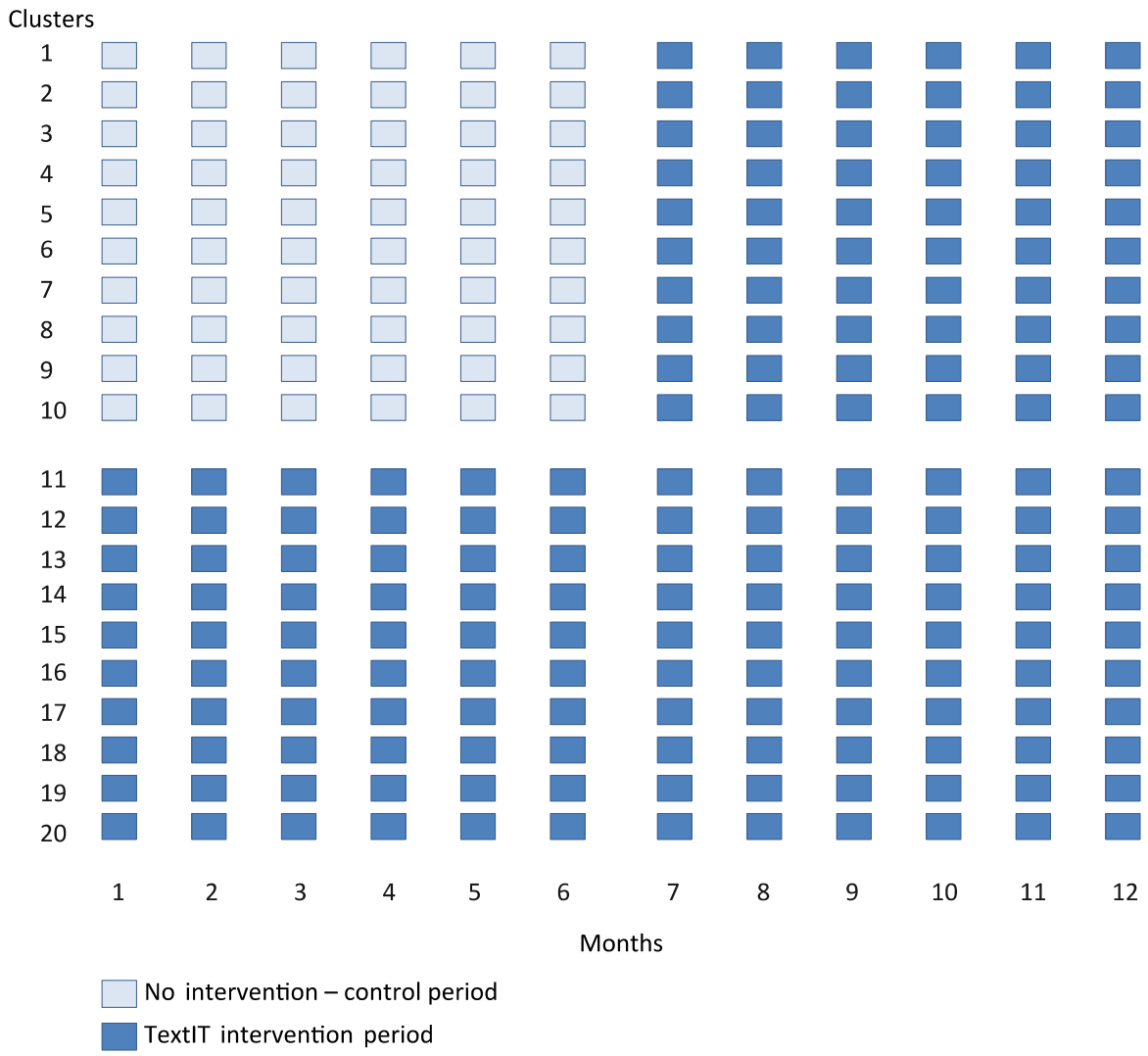

Figure 3.1. Schematic diagram of the TextIT stepped-wedge implementation design.

Exposure status for participants was determined by their period of enrollment, even though some women enrolled in phase 1 delivered after the switch to phase 2. This switch did not result in these women receiving text messages, but may have influenced staff behavior at the facilities.

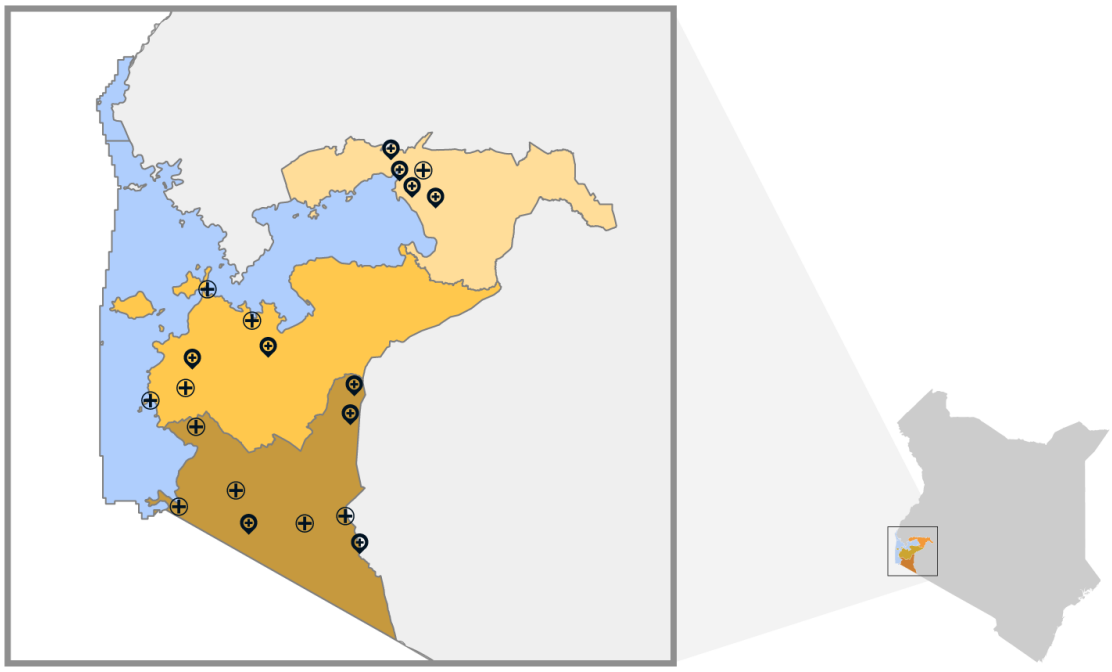

Figure 3.2. Geographical distribution of the 20 health facilities implementing TextIT in Kisumu, Migori, and Homa Bay counties in Kenya.
Key: ⊕ represent phase 1 intervention facilities; ⊕ represent phase 2 intervention facilities

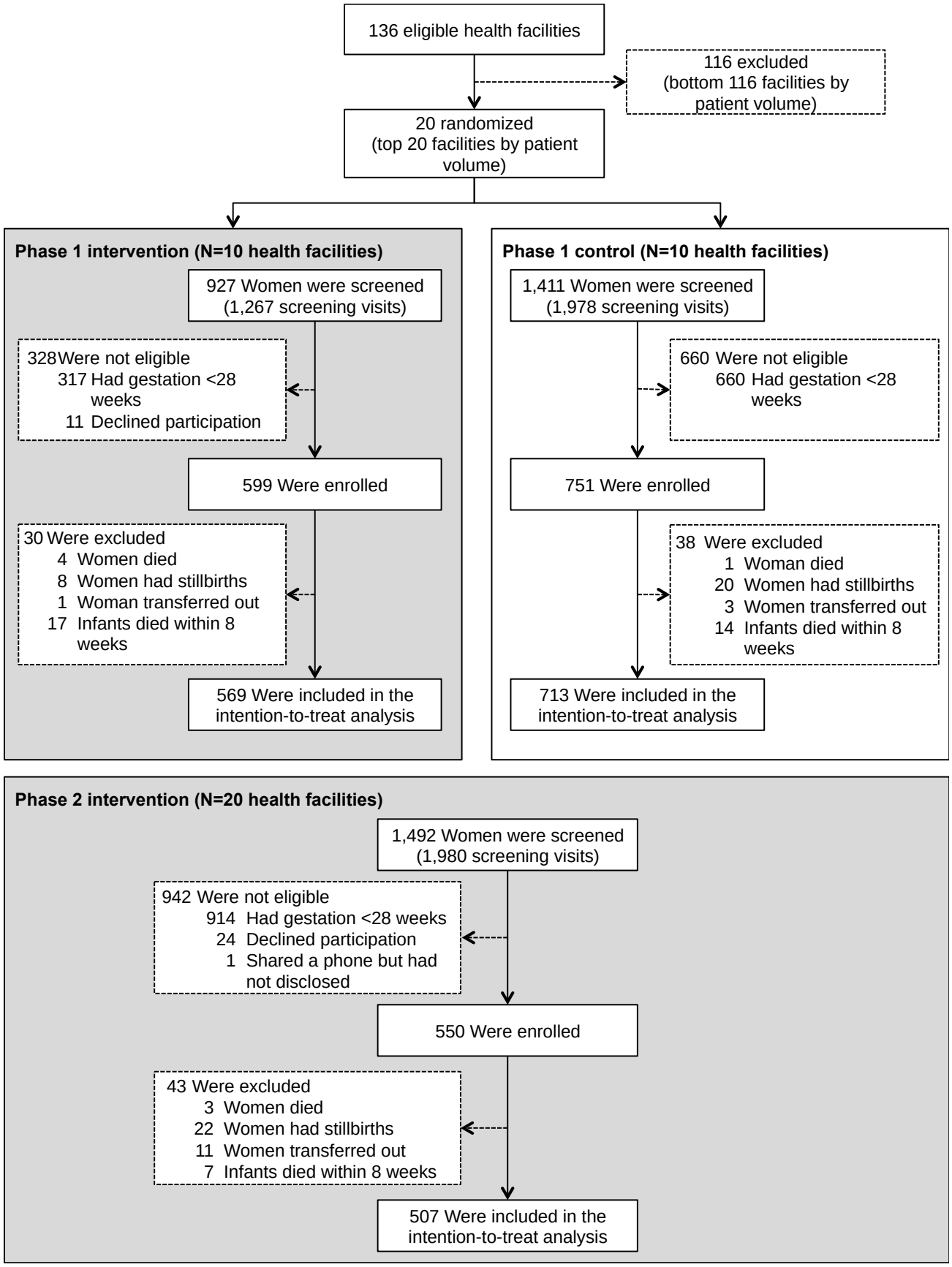

Figure 3.3. Study flow diagram. Gray background represents intervention periods; white background represents control period.

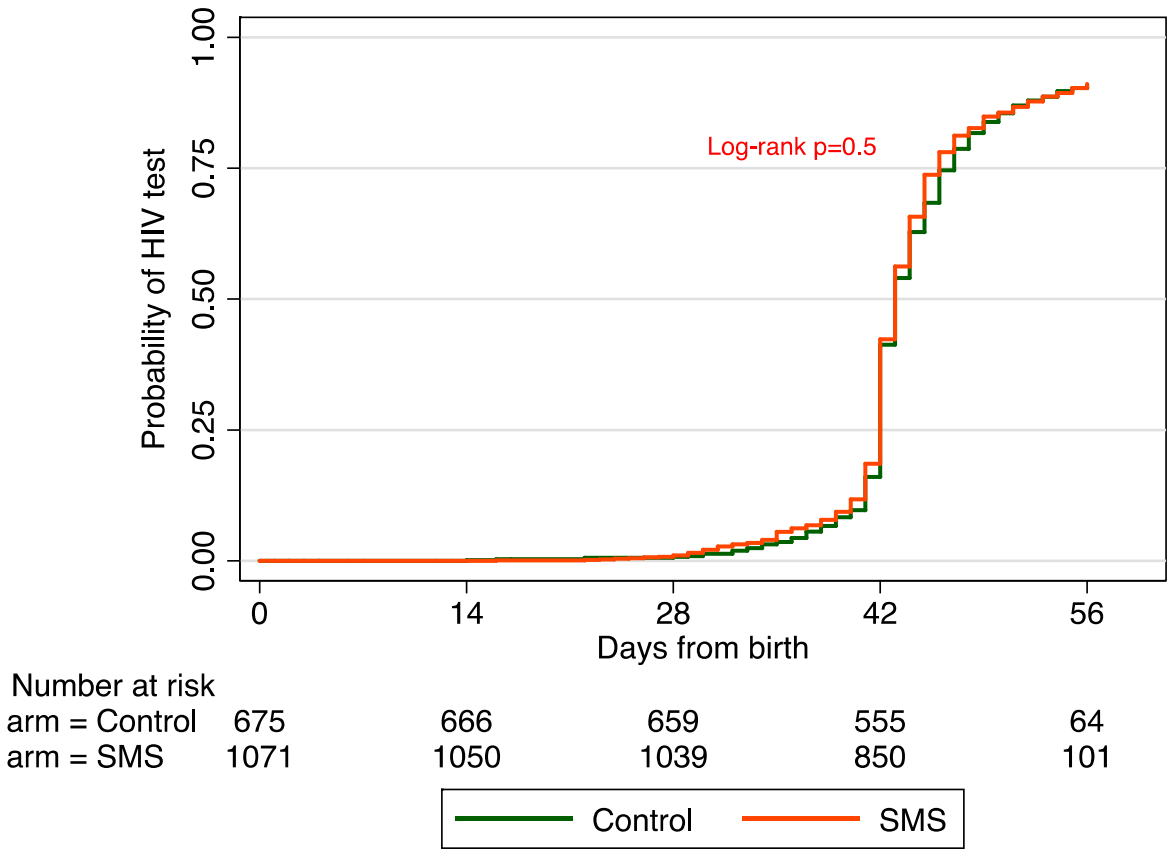

Figure 3.4. Kaplan-Meier plot showing cumulative probability of infant HIV virologic testing comparing the SMS and control groups

Table 3.6. Schedule and content of text messages included in the TextIT strategy

Gestation Week	Text message
28	Hi [name]! Congratulations for visiting clinic this week! Please call or flash 0788100133 if you have questions about your pregnancy. We're here to help you!
30	Hi [name]. We wish you a good and healthy pregnancy. We are here to support you during this journey. If you have questions please call or flash 0788100133
32	Hi [name]! We would like to wish you a good day. Please remember that if you have questions about your pregnancy, you can call or flash 0788100133
34	Good day [name]! Have you visited the mother and child care clinic lately? If not, please feel welcome to visit. Call or flash 0788100133 for questions
36	Greetings [name]! We are here for you if you have any questions about your pregnancy. Please call or flash or send a please call me to 0788100133
38	Hello [name]! Have you planned where you will deliver your baby? Please call or flash 0788100133 if you have questions or want to discuss your options
39	Hi [name], We wish you a healthy pregnancy and safe delivery! If you would like to plan your delivery, call or flash or send please call me to 0788100133
40	Hi [name], We wish you a healthy pregnancy and safe delivery! If you would like to plan your delivery, call or flash or send please call me to 0788100133
Week after delivery	
1	Dear [name], congratulations on the birth of baby [babyname]! We treasure you both! If you have questions about baby's health please call or flash 0788100133
2	Dear [name], your baby [boy/girl] will need immunization at 6 weeks of age to prevent childhood diseases and grow healthy and strong. Please call or flash 0788100133 to find out more about baby's clinic schedule. Thank you
3	Hi [name]! How are you & baby [babyname]? We know you're working hard to care for [babyname]. If you have any fever, pain or bleeding, please come to clinic
4	Dear [name], your baby [boy/girl] is now one month old. Congratulations! Please remember to have enough rest and sleep to keep yourself healthy
5	Hi [name]! How are you and baby [babyname]? Your baby needs to be immunized to prevent childhood diseases. Kindly bring baby to clinic next week. See you then!
6	Hi [name]! This week, please bring baby [babyname] to clinic for important immunizations to prevent childhood diseases and make sure [babyname] grows up healthy and strong. You will also be counselled on how to keep your baby [boy/girl] healthy

The expressions [name] and [babyname] were replaced with the woman's preferred name for herself and her baby, respectively.

Table 3.7. Maternal baseline demographic and clinical characteristics

	SMS (N=1,149) N (%)	Control (N=751) N (%)
Maternal age (years)		
<18	19 (1.7)	17 (2.3)
18-24	374 (32.6)	257 (34.2)
25-34	633 (55.1)	406 (54.1)
35+	123 (10.7)	71 (9.5)
Employed	270 (23.5)	211 (28.1)
Education		
None	158 (13.8)	54 (7.2)
Primary	721 (62.8)	536 (71.4)
Secondary	211 (18.4)	138 (18.4)
Post-secondary	59 (5.1)	23 (3.1)
Luo ethnicity (vs. other)	1085 (94.4)	710 (94.5)
Married	1026 (89.3)	697 (92.8)
First pregnancy	113 (9.8)	86 (11.5)
No previous deliveries	112 (9.7)	86 (11.5)
WHO clinical stage		
1	719 (62.6)	489 (65.1)
2	277 (24.1)	166 (22.1)
3	132 (11.5)	78 (10.4)
4	21 (1.8)	18 (2.4)
Most recent CD4 cell count (cells/μL)		
<200	98 (8.5)	61 (8.1)
200-349	180 (15.7)	152 (20.2)
350-500	249 (21.7)	180 (24)
500+	501 (43.6)	311 (41.4)
Receiving ART	1148 (99.9)	747 (99.5)
Prophylaxis for baby issued	1147 (99.8)	751 (100)
HIV test done on screening day (vs. earlier)	52 (4.5)	64 (8.5)
HIV counseling with partner	369 (32.1)	279 (37.2)

ART=antiretroviral therapy

Table 3.8. Infant characteristics at birth

	SMS (N=1,107) N (%)	Control (N=695) N (%)
Gestational age at delivery (weeks), median IQR	39 (37–41)	39 (36–41)
Live births (vs. stillbirths)	1,076 (97.2)	675 (97.1)
Female	548 (49.5)	328 (47.2)
Birth weight (kg), median (IQR)	3.2 (2.9–3.5)	3.2 (3.0–3.5)
Delivery at health facility (vs. home)	992 (89.6)	621 (89.4)
Delivery by Caesarean section	43 (3.9)	18 (2.6)
Exclusive breastfeeding (vs. other)	1,036 (93.6)	653 (94.0)

IQR=inter-quartile range

Chapter 4. THEORY-BASED MHEALTH INTERVENTION AND RETENTION IN POSTPARTUM PMTCT CARE: A CLUSTER-RANDOMIZED, STEPPED-WEDGE TRIAL

4.1 INTRODUCTION

The postpartum period is a poisoned chalice for many pregnant and breastfeeding women living with HIV. On the one hand, this period is an opportunity to crystallize the gains of PMTCT by preventing mother-to-child transmission during breastfeeding. On the other hand, it represents a significant barrier to continued care by presenting multiple unique challenges to the new mother, including breastfeeding, newborn care, return to work, and treatment adherence for both mother and baby. Across the world, adherence to antiretroviral medication (ART) poses the greatest challenge for HIV-positive women during the postpartum period [113-115]. Moreover, approximately 50% of mother-infant pairs are lost to follow-up during the postpartum period [116]. Despite these discouraging statistics, interventions to keep women engaged in postpartum HIV care are sparse, and retention remains suboptimal [116]. Optimizing this crucial part of the PMTCT cascade remains challenging for both patients and providers. In general, greater emphasis is placed on antenatal care and delivery compared to postpartum care. For example, HIV-infected women may see no need to remain in care after successful delivery, due to the misconception that the goal of treatment is solely to deliver a healthy baby [117]. Similarly, many PMTCT programs have a singular focus on antenatal care, resulting in fewer resources being invested in follow-up and retention in care during the postpartum period [118]. Low retention in postpartum care poses a major threat to successful elimination of mother-to-child HIV transmission. Across sub-Saharan Africa, an estimated 60% of all new HIV infections among children occur during the breastfeeding period [3]. The Joint United Nations Programme

on HIV/AIDS (UNAIDS) attributes this high proportion of new HIV infections to inadequate mechanisms to retain mothers in postpartum care [3], which underscores the urgent need for interventions to retain women in care during this critical period. High rates of loss to follow-up in PMTCT programs may not only attenuate the benefits of lifelong ART to individual women, but also negate the impact of preventing perinatal HIV transmission to infants.

Psaros et al., in a recent review, recommended using low cost text messages to prevent women from "falling off the cliff of the treatment cascade" after pregnancy [116]. Recent qualitative studies have shown that such mHealth approaches are acceptable and feasible for supporting PMTCT [40, 119]. In recognition of the unique opportunities presented by mHealth interventions, the Kenya Strategic Framework for Elimination of Mother-to-Child Transmission of HIV listed priority research questions that included how mobile phones could be used to improve retention in HIV care [103]. In response, we developed an interactive two-way text messaging intervention using a behavioral theoretical framework [40]. We then conducted a randomized trial that demonstrated the efficacy of this text messaging intervention, dubbed TextIT, for improving maternal retention in early postpartum HIV care [39]. In the present study, we aimed to determine the effect of TextIT on increasing the proportion of HIV-infected pregnant women who remain in care and attend a postpartum clinic visit within eight weeks of delivery under real-world, routine care conditions.

4.2 METHODS

The design, population, and procedures of this study are similar to those described in Chapter 3. These sections of the dissertation are written as freestanding chapters; therefore the methods are included below to enable a more coherent flow for this current chapter.

4.2.1 *Study design*

The TextIT study was a pragmatic, cluster randomized, stepped-wedge trial with two time periods of observation. Twenty clusters were selected for implementation. Ten clusters were randomly allocated to begin implementing the intervention immediately, while the remaining 10 began implementing approximately six months later. Figure 4.1 shows the stepped-wedge design of the TextIT study.

4.2.2 *Rationale for a cluster-randomized stepped wedge design*

We chose the cluster as the most appropriate unit of randomization because under routine care settings, public health interventions are implemented at the health facility level. This design also allowed us to capture the effects of the intervention on the health system [92], and maximized the potential for producing generalizable findings. As we had previously shown that this intervention is efficacious, equipoise was not justifiable within the same setting–this intervention would likely do more good than harm. However, due to logistical, financial, and human resource constraints, it was not feasible to expand the intervention to all facilities at the same time. The stepped wedge design addressed ethical concerns by ensuring that no targeted health facility was deprived of an efficacious and potentially effective intervention. This design also reduced the risk of "contamination" of the intervention effect. In an individually randomized design, women who are allocated to receive text messages could potentially share the messages with those allocated to the control arm at the same health facility. Additionally, staff members who are aware of on-going observation might make extra effort to counsel women and improve follow-up and record keeping (the Hawthorne effect) [93]. Both the individual-level and facility-level effects could modify behaviour among control group women, resulting in contamination. The

selected health facilities were run by the Ministry of Health. By design, these facilities were geographically spread out, so that they would be likely to capture distinct catchment areas. This reduced the likelihood of the intervention effect "spilling over" to control facilities due to interaction between women attending care at different clinics. As a result, randomization at the cluster level was intended to enhance internal validity by avoiding contamination at the individual level, minimizing a potential reduction in the effect size.

4.2.3 *Participants*

Study clusters were defined as health facilities supported by the Family AIDS Care and Educational Services (FACES) to provide PMTCT services. FACES is a PEPFAR/CDC funded HIV prevention, care and treatment program operated jointly by the Kenya Medical Research Institute (KEMRI) and the University of California, San Francisco. FACES cares for over 80,000 patients and supports 136 government health facilities, spread across three counties (Kisumu, Migori, and Homa Bay) in the Nyanza region of Kenya. This region has the highest HIV prevalence in the country (15%) [94]. Distribution of selected health facilities across the three counties is shown in Figure 4.2.

Potential participants included all HIV-positive pregnant women enrolled in the PMTCT program at target health facilities. Because this study was designed as a pragmatic trial to estimate effectiveness of TextIT under real world conditions, inclusion criteria were minimal. Women were offered the opportunity to receive text messages if they were ≥18 years or emancipated minors, and between 28 weeks gestation and delivery. Similar criteria were used to abstract data for women at control facilities. Women in the intervention group who reported sharing phones were excluded if they had not disclosed their HIV status to the person sharing the phone.

4.2.4 *Randomization*

An independent biostatistician at the University of Washington's Center for AIDS Research Biometrics Core generated the randomization sequence for each stratum and assigned clusters to the different intervention start periods. The biostatistician was not involved in any other aspects of the study. Randomization was stratified by clinic volume and experience level. Clinic volume was measured by the average number of pregnant women newly enrolled into the PMTCT program in the 12 months prior to randomization (≥50 versus <50 enrollments per month). Facilities were considered to have prior experience with TextIT if they had been part of a 6-month pilot project run by FACES immediately after release of the initial trial's results [39]. Stratification was implemented by dividing the 20 clinics into 4 strata such that clinics within each stratum had similar volume and experience. There were a total of 2, 6, 6, and 6 clinics in strata 1, 2, 3, and 4 respectively. Randomization was conducted separately within each stratum. Each clinic was assigned a random number. Clinics with low random number values (defined as less than the stratum median value) were assigned to start intervention immediately, while clinics with high random number values (greater than stratum median) were assigned to start intervention six months later. Due of the nature of the intervention and the need to inform facilities of their participation, it was not possible to blind clusters, health care providers, investigators, or individual participants to the group assignments. Health workers at control facilities were aware of the study and outcomes being evaluated, and that data were being abstracted from clinic records, but continued to provide usual care.

4.2.5 *Training of implementers at intervention health facilities*

"Mentor mothers" at each health facility abstracted data from routine clinic records and registered women to receive text messages at intervention facilities. Mentor mothers are a formal

lay cadre of women living with HIV who have recent experience in PMTCT (6 months to 2 years). They are deployed to maternal and child health clinics (MCH) to share best practices of PMTCT with their peers attending care, and are employed by health facility management boards or organizations supporting HIV care at a health facility (such as FACES) as part of the Ministry of Health-approved Kenya Mentor Mother Program [95]. Other health facility staff at the MCH reviewed patients, dispensed medication, provided counseling, obtained dried blood spot samples from HIV-exposed infants, and filled registers as part of their routine work. Phase one intervention sites were trained immediately after randomization, while phase two intervention sites were trained at the end of their control period, immediately prior to implementing the intervention. Training on the TextIT strategy targeted all service providers at the MCH, but mentor mothers played the leading role in implementation. Training was done by a team comprising the study principal investigator, study coordinator, study nurse, and the head of the FACES PMTCT program. Training was conducted in two stages. The first was a two-day, conference-based training at a central location attended only by mentor mothers. The second was a one-day, facility based training for all MCH service providers at each health facility. The two-day training for mentor mothers included didactic and practical sessions on each day. Didactic sessions on the first day included a review of PMTCT services and national guidelines, overview of the study protocol, data collection instruments, and training on research ethics. Practical sessions included role-plays on recruitment and enrolment procedures, a familiarization tour of the PMTCT services at two large health facilities, and group discussions on the day's experiences. The second day included didactic sessions on data collection using a mobile phone-based system, and how to register patients to receive SMS from the automated text messaging software. Practical sessions included role-plays on data abstraction from routine registers, and

registration into the SMS system. At the end of the two-day training, an evaluation of competence was conducted. Each mentor mother was required to obtain certification of ethics training by taking an online course following the two-day training. The second stage of training was completed onsite at each health facility. During the second phase, all MCH service providers were given an overview of the TextIT implementation protocol, data collection procedures, SMS-based participant registration, and the role of the mentor mother in implementing TextIT. This second phase also allowed trainers to meet mentor mothers and address gaps in competency that may have been identified by the evaluation that followed the initial two-day training.

4.2.6 *Interventions and study procedures*

At facilities randomized to continue usual care, women did not receive any study-related intervention. Mentor mothers at these facilities were trained in person at their respective facilities on abstracting data from health facility records as part of routine program evaluation. Because they were paid by funds from the TextIT study, they were aware of the general nature of the intervention and outcome being measured, but did not receive any other training until the end of the control period, immediately prior to implementing the intervention. When health facilities implemented TextIT, both in phase one and phase two of the study, mentor mothers were trained to provide a brief overview of the TextIT strategy, obtain verbal consent to receive the intervention, and provide a written information statement to women willing to receive messages. As with other interventions offered as part of standard care, women could ask questions, and health facility staff were on hand to respond. Baseline clinical and demographic characteristics were recorded only for women who provided informed consent, after which they were registered to receive intervention text messages. Participants were registered by sending a text message in a pre-defined format that included the participant's study identification number, date of the last

normal menstrual period, and preferred time of day and language for receiving messages. Languages available included English, Kiswahili, and Luo. Women also had the option of providing a preferred name to be included in outgoing text messages. Women attending clinics implementing TextIT who lacked phones continued to receive standard care. However, they were considered as having been exposed to the TextIT intervention in the intent-to-treat analysis.

Registered women received up to 14 text messages during pregnancy and after delivery. Messages were sent on weeks 28, 30, 32, 34, 36, 38, 39, and 40 during the third trimester of pregnancy. One message per week was sent for the first six weeks after delivery. The message content and schedule were the same as those used in the earlier study that determined the efficacy of this intervention (Table 3.6) [39]. Participants at facilities implementing TextIT had the option to respond to text messages, call, or send inquiry text messages to a designated clinic phone. One nurse was designated to respond to all calls and text messages. Participants could also request a call from the nurse by sending a free "call back" text message to the designated clinic phone at any time. If a participant requested to be called back, our automated software acknowledged the request by sending back a message in the participant's preferred language containing the text, "Thank you. A nurse will call you soon." At the same time, the software sent a message to the nurse containing the text, "Patient [name] has asked to be called at [phone number]." Upon receiving this message, the nurse called the participant and recorded details of the conversation on a standardized clinic form. An experienced clinical provider from the FACES program was available for consultation by the TextIT nurse at any time through the *Uliza!* consultation service [96]. *Uliza!* is a toll-free 24-hour telephone consultation service for HIV clinical service providers in Kenya that is run by FACES in partnership with the National AIDS and STI Control Program.

Beginning in the 37th week of gestation, mentor mothers reviewed clinic records daily to determine whether delivery had occurred at the health facility. If delivery had not occurred at the facility, the TextIT nurse called text message recipients weekly, beginning at 37 weeks, to determine whether they had delivered elsewhere. If delivery was confirmed, the nurse recorded the date, outcome, place, and mode of delivery. Additionally, the baby's sex and name were ascertained, and this information was used to update subsequent automated text messages. Where delivery had not occurred, participants were called again a week later and every week thereafter until delivery status was ascertained. In practice, most participants either sent a text message or called to report delivery. To ascertain delivery status for participants at control facilities, mentor mothers reviewed clinic records daily, beginning from the estimated date of delivery. For all participants, if no record of delivery existed at the facility at the end of the follow-up period, clinic staff obtained this information at the first postnatal contact with the mother (for women who visited the clinic). Participants at intervention facilities were offered the option to stop receiving text messages by presenting to the clinic and indicating their desire to stop, or by sending an SMS with the word 'STOP', although none did.

4.2.7 *Outcomes*

The primary outcome measure was the proportion of women retained in postpartum PMTCT. This was defined as documented return for at least one visit at the PMTCT, postnatal, or general HIV care clinic within eight weeks after delivery. In Kenya, the Ministry of Health recommends three postnatal clinic visits: one within 48 hours, another within one to two weeks, and a third at 6 weeks. We assessed maternal postpartum PMTCT retention by abstracting information from patient charts and clinic records. A woman was considered retained if there was a dated medical record documenting a clinic visit within eight weeks after delivery. We relied on a well-

established routine patient tracing mechanism to ascertain outcomes for women who did not return to clinic [97, 98]. Women who died before or during delivery, or who transferred to clinics not operated by FACES were excluded from the analysis.

4.2.8 *Statistical Analysis*

All analyses were performed using Stata software (StataCorp, College Station, TX). We described participant characteristics at baseline in control and intervention groups. Inferential analysis for the primary outcome followed the intent-to-treat principle. All participants were analyzed according to the cluster randomization group at the time of enrollment. Participants at facilities implementing the TextIT intervention were all considered to be in the intervention group, regardless of whether they received the intervention or not. Our primary analysis was on the individual-level binary response values, Y_{ijk}. The predictor of interest was treatment assignment (cluster-level values X_{ij}). Time period j was included as a covariate. A covariate for the stratum of randomization was also included [100]. Our analysis used generalized estimating equations (GEE) methods on the individual-level data to account for variable cluster sizes. Such methods are robust to misspecification of the variance structure when the "sandwich" estimate of the variance is used [99]. Specifically, we used modified Poisson regression with robust variance estimation to estimate the relative risk and 95% confidence intervals (CIs), using GEE with working exchangeable correlation structure to account for clustering by site [101]. All tests were two-sided and conducted at the 5% significance level.

4.2.9 *Ethical considerations*

County health officials provided written permission for the health facilities in their respective jurisdictions to take part in the study. All text message recipients provided verbal informed

consent to receive the messages. Upon the release of our initial randomized trial findings, FACES conducted a pilot of this intervention at six facilities for six months to determine feasibility for inclusion as part of the standard package of care. Following the pilot, FACES included the intervention as part of routine care for pregnant and postpartum women living with HIV attending care at the six health facilities where the pilot took place. However, funding constraints led to cessation of this activity in July 2014 (approximately six months prior to this TextIT expansion). Directors of the health departments in the target counties of Kisumu, Homa Bay, and Migori supported the expansion of TextIT as part of standard care. In this context, the usual practice at Ministry of Health facilities is to obtain verbal consent. As such, although this intervention was at the health facility level, we sought individual patient verbal consent for all women receiving text messages. For women at health facilities not implementing the TextIT intervention, we were not required by the institutional review boards (IRBs) to obtain individual-level consent to collect outcome data. As part of the FACES program, we had continuing approval from the relevant IRBs to collect such data that were already being captured routinely for evaluation without obtaining individual-level consent. Ethical approval was obtained from the Kenya Medical Research Institute's Scientific and Ethics Review Unit, the University of Washington's Human Subjects Division, and UCSF's Committee on Human Research. The trial is registered in ClinicalTrials.gov (#NCT02350140).

4.3 RESULTS

4.3.1 *Study participants*

The descriptive analysis of study participants is similar to chapter 3 and is re-presented here. The flow of clusters and participants through the study is reported using a diagram (Figure 4.3) modified for a stepped wedge design from the suggested "CONSORT" format for cluster

randomized trials [102]. We assessed patient volumes at all 136 health facilities supported by FACES to offer PMTCT services, and included the top 20 in the study. Database closure for this analysis was May 20, 2016. All participants who had completed follow-up by this date were included in the present analysis. Between February 11, 2015 and May 20, 2016, 3,830 women were assessed for study participation at the 20 health facilities (5,225 screening visits in total). Of these, 1,894 who were less than 28 weeks pregnant were excluded. In the intervention phase, we excluded 35 who declined participation and one who shared a phone but had not disclosed to the person sharing. Overall, 1900 women participated in the study, including 751 at step 1 control facilities, 599 at step 1 intervention facilities, and 550 in step 2 across all 20 facilities. Table 4.10 shows the baseline characteristics of women by intervention and control groups. Maternal demographic and clinical characteristics at enrollment were well balanced across both groups. Overall, the median age at enrollment was 27 years (interquartile range [IQR] 23–30), and only 36 (2%) of enrolled women were less than 18 years old. The median gestational age at enrollment was 30 weeks (IQR 28–34). The majority of women were unemployed (1,419/1,900; 75%), had completed primary education (1,257/1,900; 66%), and were married (1,723/1,900; 91%). The median CD4 cell count at enrollment was 477 cells/μL (IQR 328–670), and 13% were classified as WHO stage 3 or 4. Nearly all women (1,895/1,900; >99%) were receiving ART as part of the Option B+ program (lifelong ART for all pregnant and breastfeeding women living with HIV), and a high proportion (1,784/1,900; 94%) had been tested for HIV before the study enrollment day. There were 1,637 (86%) of 1,900 women who owned a phone. Of these, 416 (25%) reported sharing their phone and had disclosed their HIV status to the person sharing. Of the 1,900 women enrolled overall, we excluded 5 who died before delivery and 12 who

transferred before delivery to other health facilities not supported by FACES, leaving 1,883 with outcome data for analysis.

4.3.2 *Retention in postpartum PMTCT*

Overall, 1,569 (83%) of 1,883 women were retained in care during the first eight weeks after delivery, including 998 (88%) of 1,136 in the intervention group and 571 (76%) of 747 in the control group (relative risk [RR] 1.18; 95% CI 1.01–1.39; p=0.04).

4.4 DISCUSSION

This study evaluated the effect the TextIT intervention on postpartum retention in PMTCT during the first eight weeks after delivery. Under real-world, routine care conditions, TextIT led to a significant improvement in postpartum retention in PMTCT compared to standard care. There were 12% more women retained at facilities implementing TextIT compared with women at facilities providing usual care.

Retention in postpartum care has been a major challenge for PMTCT programs across sub-Saharan Africa. For example, two studies from Uganda's largest hospital both found that, under routine conditions in 2009 and 2015, only 38% of women in the PMTCT program attended a postpartum clinic appointment within eight weeks of delivery [120, 121]. By significantly improving retention rates within eight weeks of delivery, our study provides a timely response to the persistent problem of early postpartum loss to follow-up in PMTCT care. The two-way nature of our TextIT intervention provided a unique opportunity for additional patient-provider communication, beyond the communication during clinic appointments. A study in Malawi recently found that health care workers and women initiating ART under Option B+ generally desired an opportunity to engage in extended counseling about this treatment option [122].

Women enrolling into PMTCT programs rapidly initiate the Option B+ regimen without adequate counseling to prepare for lifelong ART. This feature is associated with high loss to follow-up [10]. Indeed, Shaffer and colleagues have termed the Option B+ approach a "radically condensed, life-changing event [123]" that still needs much more support to ensure its success. As the Option B+ strategy is expanded in Kenya, similar challenges are expected. The TextIT intervention provides an additional opportunity for women to have unanswered questions addressed, by phone or text message, at their convenience.

We were surprised to find that even in the control group, three quarters of women were retained. This was a much higher proportion than the 12% we observed in our earlier efficacy trial conducted in the same region [39]. A part of this increase is almost certainly related to a change in our definition of this endpoint. In the present study, postpartum follow-up appointments were ascertained at general HIV clinics in addition to PMTCT and postnatal clinics. In contrast, during the efficacy trial, postpartum visit information was obtained only from the PMTCT and postnatal clinics. Ongoing efforts to improve retention in PMTCT could further explain the rise in background retention rates in the present study compared to the earlier efficacy trial. Within the FACES program, these included interventions to improve uptake of PMTCT services [67], integrate PMTCT services with antenatal care [104], and increase male involvement in PMTCT [124]. An integrated package of similar interventions significantly improved retention in PMTCT at six weeks after delivery in a randomized trial in Nigeria [125]. Despite a rise in background rates of retention in postpartum PMTCT in our context, the TextIT intervention still increased retention rates significantly when compared with standard care.

Important gaps remain in engaging women in lifelong ART, including structural and clinic-based barriers that may not be amenable to text messaging [117, 126, 127]. As such, the

TextIT intervention should be viewed as one of a number of useful tools for addressing loss to follow-up after delivery in PMTCT programs. Other interventions have also been efficacious for improving postpartum retention in PMTCT. In the Democratic Republic of Congo, Yotebieng et al. found that cash incentives conditional on clinic attendance increased PMTCT retention at six weeks postpartum from 72% in the control group to 81% in the intervention group [128]. In Nigeria, Aliyu et al. found that a package of integrated, family-focused PMTCT services increased retention at six weeks postpartum from 9% in the control group to 83% in the intervention group [125]. The results of these two recent studies, together with those of our present study, highlight the need for context-sensitive interventions aimed at closing different gaps along the PMTCT cascade. Policy makers should apply contextual knowledge in deciding which intervention, or combination of interventions, is likely to have the greatest impact in their specific environments.

A major challenge in translating research findings into successful programs in the real world is the lack of scientifically rigorous evidence of effectiveness outside of controlled research settings. For example, a study in Uganda found that an overwhelming evidence base for efficacious interventions in HIV care existed [129]. Yet, few of those interventions had been implemented, or evaluated for effectiveness, under routine program conditions in Uganda. In the present study, we followed up our finding of efficacy of the TextIT intervention in a controlled setting with a rigorous evaluation demonstrating effectiveness under real-world, routine care conditions.

Our study had several strengths. First, we successfully leveraged the existing health system infrastructure by using routine clinic records and existing health workers to implement and evaluate the intervention. Thus, our study provided an indirect assessment of the utility of

routine data collection to assess implementation of interventions within PMTCT programs. Notably, our evaluation relied on good quality program data, which would be required in other settings planning similar evaluations. Second, the intervention text messages were personalized by gestational age, mother's name, and the infant's name and age. These features were tailored to enable women feel a "personal connection" with the clinic that might not have existed previously. Moreover, women receiving text messages could call a nurse or ask to be called back around the clock. This feature extended contact between patients and providers beyond the clinic. As such, the TextIT intervention potentially helped to address barriers to clinic attendance such as needing to re-schedule appointments, informing clinics about transfers, and generally seeking guidance on how to navigate the postpartum period. Finally, by increasing provider-patient contact without exerting an extra burden on the clinic infrastructure, our mHealth intervention could reduce the cost of delivering personalized care while achieving high patient and provider satisfaction and improved clinical outcomes.

Our study had a number of limitations. The question of sustained engagement in HIV care beyond eight weeks postpartum remains unanswered. However, our intervention significantly increased retention during the period with the highest risk of disengagement from postpartum PMTCT care. A transition to longer-term support for retention will certainly be needed to cement these gains. Also, we did not conduct an economic evaluation of this intervention. A cost-effectiveness analysis of the effect of TextIT on postpartum PMTCT retention would have provided even more robust evidence from which policy makers could draw readily actionable conclusions. To address both the question of longer term retention and the cost and budget impact of this intervention, we recently launched a follow-up study that will evaluate retention through 18 months postpartum and include a cost-effectiveness analysis.

4.4.1 *Conclusion*

Implementation science studies hold potential for rapidly expanding the successful delivery of efficacious interventions for PMTCT [130, 131]. Using an implementation science approach, our study has shown that theory-based text messaging significantly improved retention in care for women in PMTCT programs in a real-world, routine care setting. Applying an implementation science approach enabled us to understand, quantify, and bridge the gap between evidence and practice. Our findings substantially advance the field of implementation science for HIV by expanding an efficacious intervention with fidelity to the original design, and providing evidence of effectiveness under real-world, routine care conditions. Our approach and findings accelerate the understanding of what works for retention along the PMTCT cascade, and how to translate it into successful programs with public health impact. Given the adaptability, ease of integration with routine services, and widespread access to mobile phones among patients, this intervention is a “low-hanging fruit” that PMTCT programs in Kenya and across Africa could easily adopt and disseminate more broadly.

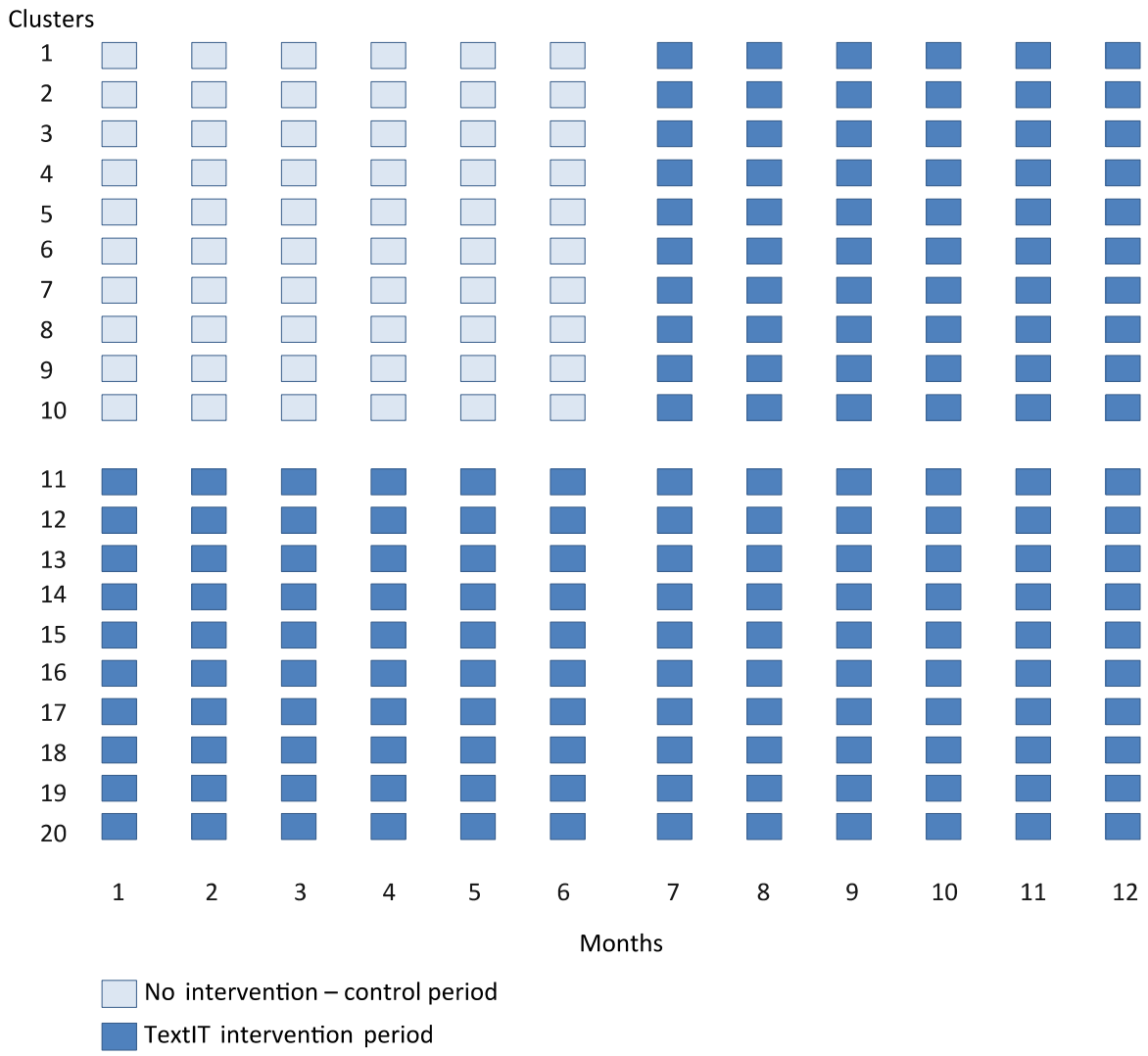

Figure 4.1. Schematic diagram of the TextIT stepped-wedge implementation design.

Exposure status for participants was determined by their period of enrollment, even though some women enrolled in phase 1 delivered after the switch to phase 2. This switch did not result in these women receiving text messages, but may have influenced staff behavior at the facilities.

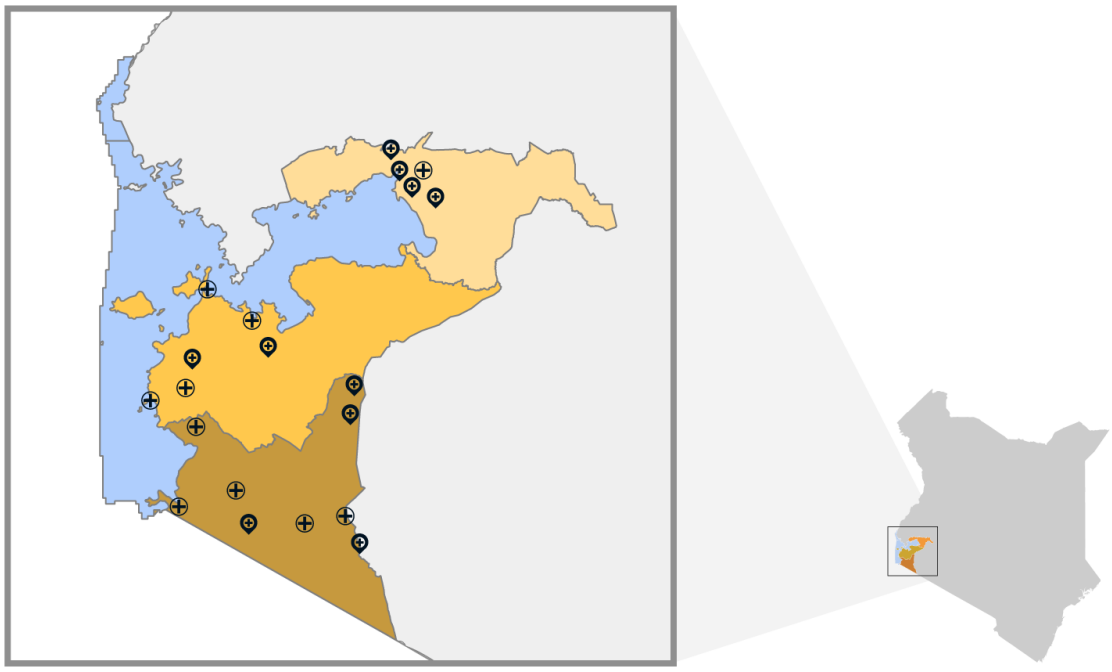

Figure 4.2. Geographical distribution of the 20 health facilities implementing TextIT in Kisumu, Migori, and Homa Bay counties in Kenya.
Key: ⊕ represent phase 1 intervention facilities; ⊕ represent phase 2 intervention facilities

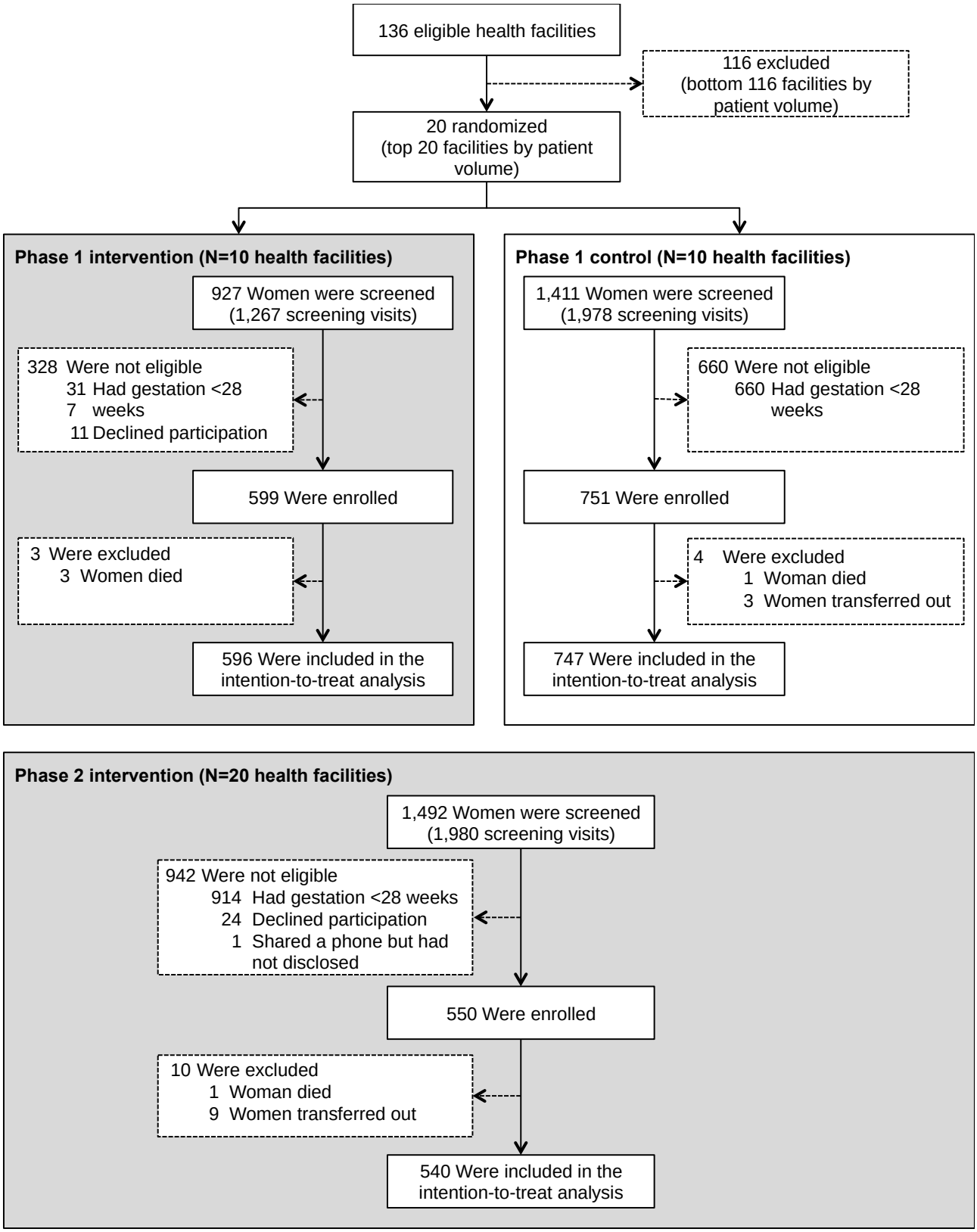

Figure 4.3. Study flow diagram. Gray background represents intervention periods; white background represents control period.

Table 4.9. Schedule and content of text messages included in the TextIT strategy

Gestation Week	Text message
28	Hi [name]! Congratulations for visiting clinic this week! Please call or flash 0788100133 if you have questions about your pregnancy. We're here to help you!
30	Hi [name]. We wish you a good and healthy pregnancy. We are here to support you during this journey. If you have questions please call or flash 0788100133
32	Hi [name]! We would like to wish you a good day. Please remember that if you have questions about your pregnancy, you can call or flash 0788100133
34	Good day [name]! Have you visited the mother and child care clinic lately? If not, please feel welcome to visit. Call or flash 0788100133 for questions
36	Greetings [name]! We are here for you if you have any questions about your pregnancy. Please call or flash or send a please call me to 0788100133
38	Hello [name]! Have you planned where you will deliver your baby? Please call or flash 0788100133 if you have questions or want to discuss your options
39	Hi [name], We wish you a healthy pregnancy and safe delivery! If you would like to plan your delivery, call or flash or send please call me to 0788100133
40	Hi [name], We wish you a healthy pregnancy and safe delivery! If you would like to plan your delivery, call or flash or send please call me to 0788100133
Week after delivery	
1	Dear [name], congratulations on the birth of baby [babyname]! We treasure you both! If you have questions about baby's health please call or flash 0788100133
2	Dear [name], your baby [boy/girl] will need immunization at 6 weeks of age to prevent childhood diseases and grow healthy and strong. Please call or flash 0788100133 to find out more about baby's clinic schedule. Thank you
3	Hi [name]! How are you & baby [babyname]? We know you're working hard to care for [babyname]. If you have any fever, pain or bleeding, please come to clinic
4	Dear [name], your baby [boy/girl] is now one month old. Congratulations! Please remember to have enough rest and sleep to keep yourself healthy
5	Hi [name]! How are you and baby [babyname]? Your baby needs to be immunized to prevent childhood diseases. Kindly bring baby to clinic next week. See you then!
6	Hi [name]! This week, please bring baby [babyname] to clinic for important immunizations to prevent childhood diseases and make sure [babyname] grows up healthy and strong. You will also be counselled on how to keep your baby [boy/girl] healthy

The expressions [name] and [babyname] were replaced with the woman's preferred name for herself and her baby, respectively.

Table 4.10. Maternal baseline demographic and clinical characteristics

	SMS (N=1,149) N (%)	Control (N=751) N (%)
Maternal age (years)		
<18	19 (1.7)	17 (2.3)
18-24	374 (32.6)	257 (34.2)
25-34	633 (55.1)	406 (54.1)
35+	123 (10.7)	71 (9.5)
Employed	270 (23.5)	211 (28.1)
Education		
None	158 (13.8)	54 (7.2)
Primary	721 (62.8)	536 (71.4)
Secondary	211 (18.4)	138 (18.4)
Post-secondary	59 (5.1)	23 (3.1)
Luo ethnicity (vs. other)	1085 (94.4)	710 (94.5)
Married	1026 (89.3)	697 (92.8)
First pregnancy	113 (9.8)	86 (11.5)
No previous deliveries	112 (9.7)	86 (11.5)
WHO clinical stage		
1	719 (62.6)	489 (65.1)
2	277 (24.1)	166 (22.1)
3	132 (11.5)	78 (10.4)
4	21 (1.8)	18 (2.4)
Most recent CD4 cell count (cells/μL)		
<200	98 (8.5)	61 (8.1)
200-349	180 (15.7)	152 (20.2)
350-500	249 (21.7)	180 (24)
500+	501 (43.6)	311 (41.4)
Receiving ART	1148 (99.9)	747 (99.5)
Prophylaxis for baby issued	1147 (99.8)	751 (100)
HIV test done on screening day (vs. earlier)	52 (4.5)	64 (8.5)
HIV counseling with partner	369 (32.1)	279 (37.2)

ART=antiretroviral therapy

Chapter 5. FITTING TEXTIT TO THE RE-AIM FRAMEWORK FOR IMPLEMENTATION SCIENCE

Our stepped wedge trial has enabled a more in-depth understanding of the effectiveness and limitations of the TextIT intervention in a real-world, routine-care setting. Edwards and Barker emphasize the importance of characterizing context when describing implementation strategies [132]. Simple interventions, such as the TextIT strategy, could magnify the benefits of PMTCT if implemented within the appropriate context [133]. Glasgow et al. recommend using theoretical models of implementation for health interventions that incorporate technology (eHealth/mHealth) to enable more efficient integration into practice [134]. Therefore, we applied an implementation science framework to make the TextIT strategy amenable to potential adoption, adaptation, or scale-up in similar contexts within Kenya and across Africa. Specifically, we used the RE-AIM framework–Reach, Effectiveness, Adoption, Implementation, and Maintenance–whose constructs summarize what we feel are important dimensions of rapidly translating research on an efficacious mHealth intervention into practice in a high HIV prevalence, resource limited setting [135, 136]. This approach has been used to plan for, and evaluate, the dissemination of other public health interventions [44, 137]. To achieve fidelity to the RE-AIM implementation model, we report our evaluation according to the criteria for "fully developed use" of RE-AIM, as proposed by Kessler et al [137]. The effect of the TextIT intervention was attributable to the text messaging component (automated text messaging system; message content, frequency, and timing; and individual message tailoring), and the resources and processes for delivering the intervention (improved data collection systems, adherence to standard care recommendations for PMTCT service delivery, and promoting

awareness among health workers about ongoing monitoring). However, we restricted our RE-AIM evaluation to the text messaging component as it was the most amenable for such an evaluation.

Reach refers to the level of penetration of an intervention in terms the proportion of eligible participants who receive the intervention [138]. For the TextIT strategy, the denominator was the estimated target population of HIV-positive pregnant women with gestation ≥28 weeks or who delivered on the day of enrollment. By engaging existing providers rather than study-specific staff to invite patients to receive the intervention, our study was designed to contact a high proportion of these women for participation. Those who declined participation were still included in the denominator. The numerator was the total number of women who were enrolled for the TextIT strategy. We contacted 2,419 women at facilities offering the TextIT intervention. Of these, 1,185 were eligible to receive the intervention (target population) and 1,234 were excluded due to gestation <28 weeks. Among those eligible, 36 declined to receive messages and the remaining 1,149 were enrolled, resulting in 97% (1,149/1,185) reach.

Effectiveness–an intervention's impact on targeted outcomes–was the effect size of TextIT on the primary outcomes of infant HIV testing and maternal retention in postpartum PMTCT. The absolute difference comparing the TextIT and control periods for infant HIV testing was 3.9% (95% CI -1.8%–9.5%). The overall proportion of infants tested for HIV (88%) in the intervention time period was still lower than the 90-90-90 target of testing at least 90% of HIV-exposed infants. The absolute difference comparing the TextIT and control periods for maternal retention in postpartum PMTCT was 14% (95% CI 2%–26%). To gain additional insight into effectiveness of TextIT for maternal retention in care, we calculated the number

needed to treat to be 7. That is, we would need to register 7 women into the TextIT intervention to retain one additional woman.

Adoption was measured as the proportion of health facilities in which the TextIT strategy was implemented out of all the health facilities initially approached to take part. We approached 20 health facilities in three counties, and all implemented the strategy (100% adoption). Characteristics of participating health facilities according to intervention period are presented in Table 5.11. We did not measure adoption at the staff level because only one member of staff per health facility (a "mentor mother") was required to implement the intervention. This perfect adoption proportion by health facilities was due to a combination of strategies including regular meetings with county health management teams, dissemination of results of the initial efficacy trial at numerous stakeholder meetings at national and local level, and identifying and working closely with opinion leaders within county health management teams to support adoption. This approach to dissemination was consistent with the Diffusion of Innovations theory by ensuring that stakeholders were provided with adequate knowledge, were persuaded by the merits of the intervention, had the authority to make policy decisions, and could spread knowledge about the intervention through their own professional and social networks [139].

Implementation, defined as delivery of the TextIT intervention with fidelity to the original design, was measured at the participant level as the proportion of women registered to receive messages to whom messages were successfully delivered as scheduled. We determined this from automated reports of outgoing text messages generated by our TextIT software. Women were registered to receive messages at different gestational ages, and their message schedule was pegged to the estimated date of delivery (EDD). However, if they had not delivered by the EDD, the last message was resent weekly until they delivered. Therefore, retrospectively,

the expected number of messages was equal to the total number of text messages sent out by the automated system. The text messaging system included a record indicating whether a message was successfully delivered or not. We included both successfully and unsuccessfully delivered messages in the denominator for measuring implementation fidelity. Messages that were not successfully delivered were considered failure and were not included in the numerator. Thus, we calculated the number of messages successfully delivered (numerator) as the difference between the total number of messages sent out by the automated text messaging system and the total number of failed messages. There were 1,149 women enrolled in the intervention group at different gestational ages, including 135 who did not have phones and could therefore not receive text messages. The total number of messages sent out, including failed messages, was 17,517. The median number of messages per woman was 18 (IQR 1–23). A total of 54 messages were sent but not delivered to recipients (failed messages), resulting in 99.7% fidelity. Reasons for delivery failure included inactivated phone numbers, phones out of network connectivity range, and phones switched off. To provide a program level measure of implementation success, we included in the denominator the 135 women who did not have access to a phone and yet were considered to have received the intervention. We assigned each woman the median number of messages (18) for a total of 2,430 additional messages. We included these additional messages in the denominator and conducted a sensitivity analysis assuming all were failed messages. The overall proportion of messages successfully delivered fell to 75.4%. We also calculated the costs associated with this level of implementation fidelity (Table 5.12). We estimated spending approximately $264 for the text messaging system, including the cost of sending messages and responding to callback requests. We also calculated the cost of human resources needed to deliver the intervention as approximately $55,590, including the monthly salaries of a nurse,

coordinator, and 20 mentor mothers. Therefore, the total estimated cost of delivering the intervention over 17 months was $55,590.

Maintenance at the health facility level, defined as the sustainability or institutionalization of the TextIT strategy, was somewhat difficult to ascertain during the limited interval of our study. Kessler and colleagues recommend measuring maintenance according to four criteria [137]. The first is whether the "program is still ongoing at ≥6 months post study funding." Funding for the TextIT study ended in February 2016 but implementation is ongoing, supported by the FACES program. Up to the point of writing this dissertation (June 2016), the program has been ongoing for 3 months after expiry of funding. The second criterion for measuring maintenance relates to whether the "program was adapted long term." At the end of the funding period, we measured the proportion of health facilities that would be supported by the PEPFAR-funded FACES organization to continue implementing the TextIT intervention. We considered a facility "supported" for TextIT continuation if the FACES organization funded employment of a mentor mother to continue enrolling women to receive the intervention after funding for the existing TextIT mentor mothers expired in February 2016. The FACES organization employed 20 of 20 mentor mothers (100%), one per health facility, to support TextIT continuation. The third criterion for measuring maintenance is, "Some measure/discussion of alignment to organization mission or sustainability of business model." The FACES organization has included this intervention as part of its standard care package of PMTCT. The FACES grant application for renewal of PEPFAR funding expected in September 2016 includes an expansion of TextIT implementation across all 132 health facilities supported by the program. At the national level, the Kenya National AIDS and STI Control Program (NASCOP) included the TextIT intervention in the most recent (2016) national "Best Practices

Manual" for HIV care. We also aimed to measure the proportion of health facilities that included the TextIT strategy in their annual operating plan (AOP) for the financial year following the formal conclusion of the study. The AOP is a resource planning document that each health facility is required to prepare every year to budget for the following year's activities. However, following the devolution of public health facility management in Kenya to the county level, it has become difficult to obtain this information at the health facility level. We will continue to pursue this information. The final criterion for measuring maintenance is, "Use of qualitative methods data to understand setting-level institutionalization." Due to funding constraints, we did not conduct formal qualitative research at the health facility level.

An important strength of using the RE-AIM framework as a guidepost along the pathway from efficacy research to large-scale implementation is the ability to both evaluate the stepped-wedge expansion and act as a tool for planning broader expansion. We are among the first in this field to evaluate and plan for scale up of a PMTCT intervention using the RE-AIM framework. Therefore, our findings form a basis for future comparisons when the TextIT intervention is expanded to other regions in Kenya, or elsewhere in sub-Saharan Africa.

A limitation of our use of the RE-AIM framework is the lack of qualitative research to better understand each RE-AIM dimension. While a mixed methods approach would have provided additional insight into implementation, we were unable to carry out interviews due to limited funding. Our approach could have been further fortified by pairing with a broader "meta-theoretical" framework of implementation science, such as Green's Predisposing, Reinforcing and Enabling Constructs in Educational Diagnosis and Evaluation (PRECEDE) [140], or Damschroder's Consolidated Framework For Implementation Research (CFIR) [141]. These frameworks would have broadened the scope of our intervention to target health system as well

as patient-level determinants of the gap. As recently demonstrated by Gimbel and colleagues, meta-theoretical frameworks for implementation can be pivotal in contextualizing interventions and fostering widespread implementation [142]. However, the flexibility of our RE-AIM evaluation and planning approach is appealing in that it allows room for adaptation of the TextIT intervention to different contextual environments while preserving the core components of the strategy.

5.1.1 *Conclusion*

Using the RE-AIM framework has enabled a more complete understanding of different domains of the TextIT intervention as a public health tool. This work has illustrated several points. First, the TextIT intervention can reach a high and representative proportion of the target population. Second, TextIT is effective for improving maternal postpartum retention in PMTCT care under real-world routine care conditions. Third, health facility authorities have quickly adopted TextIT. Fourth, the intervention may be implemented effectively across a range of health facility settings similar to the clinics included in our study, and can be delivered with fidelity to the original design. Finally, TextIT has the potential for sustainability over time. These features, in our view, demonstrate readiness for broader dissemination. It is an intervention that, if disseminated widely, could have substantial public health impact for maternal retention in postpartum PMTCT care.

Table 5.11. Health facility characteristics

	Intervention phase 1	Intervention phase 2
Level of facility		
District hospital	3	3
Sub-district hospital	2	1
Health center	3	6
Dispensary	2	0
Number of health workers by cadre		
Mentor mothers	30	24
Nurses	217	154
Clinical officers	83	70
Lab technologists	53	54
HIV testing and counseling officers	41	34
Pharmacy technicians	35	33
Medical doctors	26	17
Clinic and community health assistants	24	32
Peer educators	22	35
Health records and information officers	21	17
Patient trackers	20	21
Nutritionists	11	12
Physiotherapists	6	14
Managing authority		
County	9	10
Non-governmental organization	1	0
Urban location (versus rural)	4	4
Total catchment population	186,244	177,176

Table 5.12. Estimated cost of implementation

Item	Units (#messages or minutes)	Unit cost (USD)	Total cost (USD)
Text messages and phone calls			
Intervention messages to participants (outgoing)	17,517	0.01	175.20
Registration messages (incoming)	1,887	0.01	18.87
Registration confirmation messages (outgoing)	1,887	0.01	18.87
Participant messages and call-back requests (incoming)	1,094	0.01	10.94
Duration of phone calls to participants (outgoing; minutes)	1,002	0.04	40.08
Sub-total			263.96
Human resources			
TextIT study nurse (number of months, monthly salary)	17	620	10,540.00
TextIT coordinator (number of months, monthly salary)	17	650	11,050.00
Mentor mothers (number of person-months, monthly salary)	340	100	34,000.00
Sub-total			55,590.00
TOTAL			55,853.96

Incoming messages refer to text messages sent to the automated system; outgoing messages refer to text messages sent by the automated system

Chapter 6. CONCLUSION

Implementation science aims to "…understand the scale of, reasons for, and strategies to close the gap between evidence and routine practice for health in real-world contexts [43]." We applied this approach to bridge the gap between what was known to be efficacious for improving infant HIV testing and maternal retention in postpartum PMTCT (theory-based text messages), and what was implemented as routine PMTCT practice in Kenya. The NIH-PEPFAR PMTCT Implementation Science Alliance promotes such approaches to translating evidence into practice as a means to catalyze much broader "adoption, adaptation, integration, scale-up, and sustainability of evidence-based interventions [112]." Our approach included research to understand the strengths and limitations of the TextIT intervention followed by phased implementation and scale-up as part of routine PMTCT care.

In Chapter 2, we used a novel study design to provide strong evidence of a "trial effect." Specifically, we showed that women enrolled in a randomized trial and randomly allocated to receive the control condition had significantly higher uptake of infant HIV testing compared to the background population of those screened but not enrolled. The exploration of routine clinic records to enable analysis in Chapter 2 highlighted key gaps in routine data collection for PMTCT. These gaps could potentially be barriers to adoption, implementation, and routine evaluation of evidence-based interventions. Understanding and overcoming these barriers could strengthen the overall health system by addressing structural PMTCT challenges and enabling real-world evaluations of PMTCT interventions, including future implementations of TextIT.

One important barrier was the poor quality of data collected for routine care. In a recent review of challenges with routine data sources for monitoring PMTCT programs in East Africa, Gourlay et al. encountered similar difficulty in obtaining complete and accurate clinic records

[89]. One reason for poor data quality was that different components of PMTCT services were offered at different physical locations within the same facility. In our study, PMTCT services were located at the antenatal clinic (maternal HIV testing, post-test counseling), PMTCT clinic (ART initiation, infant dried blood spot sample collection for HIV testing), and an offsite central laboratory (infant HIV virologic testing). This resulted in difficulty capturing data and linking mother-baby pairs through the PMTCT cascade.

A second barrier to improving PMTCT services was that routine data collection for PMTCT in Kenya relied on several unique sources. These included antenatal clinic registers (ANC), comprehensive care clinic patient charts, maternity registers, post-natal clinic registers, mother-baby booklets, HIV-exposed infants (HEI) registers, and HEI cards. The task of recording data on multiple registers, often with duplicate information, imposed an extra burden on an already stretched clinic workforce. Not surprisingly, this often led to incomplete data collection. Moreover, some health facilities had more than one version of a particular register, or made manual modifications to existing registers. For example, some facilities used both the new "longitudinal" ANC register that enabled prospective follow-up of women through pregnancy, and the older "cross-sectional" ANC register at the same time. Other facilities lacked staff members trained or experienced in using the most recent data collection tools. These problems were a result of successive changes to Kenyan PMTCT guidelines to keep up with new research and evolving WHO recommendations, a situation also witnessed in other sub-Saharan African countries [89, 143].

A final barrier to improving PMTCT services was the difficulty in linking records across multiple data sources in PMTCT programs. A substantial proportion of missing records in our study were due to inability to link clinic identifiers (IDs) across multiple data sources, despite a

thorough search. This was caused by a number of factors. For example, some women sought care at study sites but used IDs issued at non-study clinics. In some infant records, the mother's clinic ID was missing because there was no provision for this ID in infant registers, and the standard practice was to write it in by hand. We were also unable to distinguish between PMTCT IDs and ANC IDs where the numbering systems for PMTCT and ANC clinics were similar, and a woman was assigned only one of the IDs. Electronic medical records with unique patient IDs are a promising remedy for these problems [88], but are yet to be widely implemented for PMTCT services in Kenya [144, 145].

In summary, the exploration of routine data to enable the analysis in Chapter 2 revealed important barriers that could hinder the adoption, implementation, and real-world evaluation of PMTCT interventions. Our analysis in Chapter 2 enabled a deeper understanding of the components and effect of the TextIT intervention, strengthened the evidence supporting implementation to a broader population, and highlighted important structural barriers and health system deficiencies that remain to be overcome.

In Chapters 3 and 4, we used a cluster-randomized stepped-wedge implementation design to scale up the intervention to 20 public health facilities and evaluate its effectiveness in real world settings. We embedded implementation activities within routine care, and targeted all HIV-infected pregnant women in their third trimester, eliminating the more restrictive inclusion criteria from the earlier efficacy trial.

In Chapter 3, we did not find sufficient evidence of effectiveness of the intervention for improving rates of early infant HIV testing. This was largely due to unexpectedly high infant HIV testing rates in the control arm as a result of concerted efforts to beat the 2015 deadline for elimination of mother-to-child HIV transmission. Timely infant HIV testing remains crucial to

the success of the 90-90-90 goals for HIV-infected children and adolescents [146]. There is an emerging burden of undiagnosed HIV infection acquired perinatally among adolescents, many of whom present to care with serious complications of HIV [147, 148]. This gap represents a missed opportunity to identify HIV-infected children during infancy, initiate timely ART, and avoid complications of HIV infection. While TextIT was not effective for this outcome, it could still be evaluated for effectiveness in regions where infant HIV testing rates are low. In addition, we recognize that improving uptake of infant HIV testing is but one cog in the complex overall process of successful identification of HIV-infected infants. Other programmatic challenges with infant HIV testing remain unaddressed, including high clinic volumes with poor staffing [149] and inadequate case finding of HIV-exposed infants outside of PMTCT clinics [150]. These could be addressed by approaches such as using trained lay health workers to find and test HIV-exposed infants [151], extending infant HIV testing points to immunization clinics and inpatient settings [152, 153], and introducing HIV virologic testing at birth [47, 48]. Essajee et al. suggest that these approaches could play an important role in closing the testing gap and achieving the first "90" for children [152]. Resource constraints that limit the success of EID programs will also need to be addressed. For example, the requirement for high-level facilities and expertise to perform testing could potentially be eliminated with the introduction of point-of-care diagnostics [49, 50]. Finally, despite the push to introduce and scale up sophisticated technologies, simple interventions to improve existing health systems could play a major role in ensuring the success of PMTCT, including better record keeping, according respect to pregnant women who attend care, and strengthening tracing of losses to follow-up.

In Chapter 4, we found strong evidence of effectiveness of the TextIT intervention for improving maternal retention in postpartum HIV care. This was despite the challenges of

implementing a new intervention under routine conditions (including high patient volume, few and demotivated staff, subpar record keeping, and changing guidelines). Interestingly, the proportion of control group women bringing their children for HIV testing within eight weeks after delivery in Chapter 3 (84%) was higher than the proportion of control group women returning to clinic within two months in Chapter 4 (76%). This could be attributed to higher motivation among women to obtain care for their children than for themselves. For example, in our formative qualitative work to design the TextIT intervention [40], women indicated higher intrinsic motivation to bring their children to clinic after delivery than to attend their scheduled appointments. In the context of Option B+, reduced motivation to attend care after a healthy delivery has also been identified as a major reason for loss to follow-up after delivery [117].

Overall, the combined results of Chapters 2 and 3 could be interpreted as showing that simply paying more attention to EID within PMTCT programs can achieve fairly high rates of testing even without the SMS part of the intervention. The results in Chapter 4 go a step further, showing that the SMS component of the intervention can be a powerful adjunct to a functional health system to bolster maternal retention in early postpartum PMTCT care. Finally, in Chapter 5, we applied an implementation science framework, RE-AIM, to provide salient information to support broader implementation of TextIT for improving maternal retention in postpartum PMTCT care.

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