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The effect of a text-messaging intervention on retention in care for women living with HIV and their infants in Kenya

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The effect of a text-messaging intervention on retention in care for women living with HIV and their infants in Kenya

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To people living with HIV,

and to the people who care for them and help to make their lives better.

GIVE A CHILD LOVE, LAUGHTER AND PEACE, NOT AIDS.

- *Nelson Mandela*

POPULAR SCIENCE SUMMARY OF THE THESIS

Human immunodeficiency virus (HIV) can lead to acquired immunodeficiency syndrome (AIDS) and death if it is not treated with antiretroviral therapy (ART). Access to ART has improved in Africa during the last 20 years, and people with HIV can today live healthy lives on lifelong ART. In addition, the risk of HIV transmission from mother to child during pregnancy, delivery, and breastfeeding is very low for women on sustained ART. There is a problem, however, that many women stop ART and do not return for follow-up care due to denial, fear that other people will find out about their HIV infection, or other reasons. This dropout of care increases the risk of AIDS and HIV transmission from mothers to their children. This thesis aims to increase knowledge of whether mobile phone communication can prevent dropout from HIV care during pregnancy, childbirth, and breastfeeding. We also want to shed light on women's openness about their HIV infection, and their social concerns related to attending clinic appointments and taking ART.

We conducted a study where women living with HIV in Kenya got either (I) usual care to prevent HIV transmission to their children, or (II) usual care together with weekly text messages asking, "How are you?" ("Mambo?" in Swahili), until 24 months after delivery. Women were asked to send a text response indicating that they were "okay" ("sawa" in Swahili) or had a "problem" ("shida" in Swahili). Those who reported a problem or did not respond were called by telephone for support and to sort out problems.

In the first paper, we observed that a higher proportion of pregnant women had told their partner about their HIV infection compared to earlier studies from Kenya. We observed that younger women appeared to be more open about their HIV infection compared to older women, which could indicate more openness about HIV in younger couples. However, women who reported concerns about isolation or lack of support from family or friends, and concerns about separation or conflict with a partner, were less open about their HIV infection. Our results suggest that healthcare workers should consider supporting pregnant women regarding these concerns to further increase openness about their HIV status to a partner.

In the second and third paper, we observed no significant effect of text messaging on the proportion of infants who were brought back for an HIV test by eight weeks of age, or on the proportion of women and children who were still in care 18 months after delivery. We did, however, observe an overall lower-than-expected dropout of care in both study groups. Dropout of care to prevent HIV transmission from mother to child has decreased in many African countries in recent years, most likely due to improved treatment programmes.

In the fourth paper, we observed a modest use of the intervention to send "problem" and "okay" text responses. Women with lower education and younger age were less likely to send text responses, which should be considered in the planning of future text-messaging studies aimed at supporting women in care to prevent HIV transmission to their children. Many women did, however, report that the text messaging had been helpful, mainly by improving access to and communication with healthcare workers at their clinics.

ABSTRACT

Background: Retention in prevention of mother-to-child transmission (PMTCT) of HIV care is crucial to reduce vertical HIV transmission, and to improve the health and survival of women living with HIV and their infants. HIV-related stigma, social concerns, and non-disclosure of HIV status are barriers to participate in PMTCT care, which potentially could be addressed by supporting women with an interactive text-messaging intervention. The aim of this thesis was to increase knowledge of the effect of an interactive text-messaging intervention on retention in PMTCT care, and to shed light on pregnant women's HIV status disclosure and their social and emotional barriers to participate in PMTCT care in Kenya.

Methods: We recruited pregnant women living with HIV to a randomised controlled trial at six antenatal care clinics in western Kenya between June 2015 to July 2016. The participants in the intervention group received weekly text messages until 24 months postpartum, to which they were requested to respond within 48 hours if they were okay or if they had a problem. Interview data collected at study enrolment at four of the clinics were used to investigate participants' social concerns to participate in PMTCT care and their association to HIV status disclosure (paper I). We compared the uptake of early infant HIV testing (paper II), and 18-month retention in PMTCT care (paper III) between the intervention and control group at all six clinics. We also investigated women's adherence to respond if they were okay or had a problem in a cohort study of the intervention group participants (paper IV).

Results: In paper I, we observed that 80% of the women who were married or living with a partner had disclosed their HIV status to their partner. Women 35-44 years old had lower odds of HIV status disclosure to a partner (odds ratio [OR]: 0.15; 95% confidence interval [CI]: 0.05-0.44) compared to women 18-24 years old. Women reporting concerns about isolation or lack of support from family or friends (OR: 0.33; 95% CI: 0.12-0.85), separation from a partner (OR: 0.17; 95% CI: 0.05-0.57), or conflict with a partner (OR: 0.18; 95% CI: 0.05-0.67) had lower odds of HIV disclosure to a partner. In paper II we observed no effect of interactive text messaging on uptake of early infant HIV testing in the intervention group compared to the control group (rate ratio [RR]: 0.99; 95% CI: 0.90-1.10; p=0.89). In paper III, 18-month retention in care was similar in the intervention (70%) and the control group (69%) (RR: 1.02; 95% CI: 0.92-1.14; p=0.70). In paper IV we observed that women in the intervention group responded to 49% of the text messages sent to them (48% were okay responses and 1% were problem responses). Women 18-24 years old (OR: 2.20; 95% CI: 1.03-4.72) were more likely to respond to <50% of the text messages compared to women 35-44 years old. Women with higher education (OR: 0.28; 95% CI: 0.13-0.64) were less likely to respond to <50% of the text messages compared to women with lower education. Among the 59% of women who were interviewed at the end of the intervention, 95% reported that the intervention had been helpful, mainly by improving access to and communication with healthcare providers.

Conclusion: Younger women were more likely to disclose their HIV status to a partner, possibly indicating lower HIV-related stigma in younger generations in Kenya. However, our

results suggest that concerns about isolation, lack of support, separation, and conflict with a partner still prevail and may be barriers that should be addressed to further increase women's HIV status disclosure to partners. Our results suggest that interactive text messaging does not improve the uptake of early infant HIV testing or 18-month retention in PMTCT care. The modest use of the intervention to report a problem and sending weekly responses, particularly among women of lower education and younger age, should be considered in the design of future interventions aiming to improve outcomes of PMTCT care. Interactive text messaging may be useful to improve access to and communication with healthcare providers for women in PMTCT care.

LIST OF SCIENTIFIC PAPERS

The papers will be referred to in the text as paper I-IV.

I. **Björn Nordberg**, Erin E Gabriel, Edwin Were, Eunice Kaguiri, Anna Mia Ekström, Anna E Kågesten, Susanne Rautiainen.
Social concerns related to HIV status disclosure and participation in the prevention of mother-to-child transmission of HIV care among pregnant women in Kenya. *BMC Pregnancy and Childbirth, 2020, 20:225.*

II. **Björn Nordberg**, Winfred Mwangi, Mia Liisa van der Kop, Edwin Were, Eunice Kaguiri, Anna E Kågesten, Erin E Gabriel, Richard T Lester, Jonathan Mwangi, Anna Mia Ekström, Susanne Rautiainen.
The effect of weekly interactive text-messaging on early infant HIV testing in Kenya: a randomised controlled trial (WelTel PMTCT). *Scientific Reports, 2021, 11:22652.*

III. **Björn Nordberg**[*], Mia Liisa van der Kop[*], Jonathan Mwangi, Eunice Kaguiri, Katrine J Chamorro de Angeles, Richard T Lester, Erin E Gabriel, Susanne Rautiainen, Patricia Awiti, Anna E Kågesten, Edwin Were[†], Anna Mia Ekström[†].
The effect of an interactive weekly text-messaging intervention on retention in prevention of mother-to-child transmission of HIV care: a randomised controlled trial (WelTel PMTCT). *(Submitted).*

IV. **Björn Nordberg**, Eunice Kaguiri, Erin E Gabriel, Mia Liisa van der Kop, Katrine J Chamorro de Angeles, Winfred Mwangi, Richard T Lester, Edwin Were, Anna Mia Ekström, Susanne Rautiainen.
The use, adherence, and evaluation of interactive text messaging among women admitted to prevention of mother-to-child transmission of HIV care in Kenya (WelTel PMTCT). *(Manuscript).*

CONTENTS

LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AMPATH	Academic Model Providing Access to Healthcare
ANC	Antenatal care
ART	Antiretroviral therapy
CI	Confidence interval
EID	Early infant diagnosis
EMTCT	Elimination of mother-to-child transmission
HEI	HIV-exposed infant
HIV	Human Immunodeficiency Virus
IQR	Interquartile range
mHealth	Mobile Health
MTCT	Mother-to-child transmission
MTRH	Moi Teaching and Referral Hospital
NASCOP	National AIDS and STI Control Programme
OR	Odds ratio
PCR	Polymerase chain reaction
PEPFAR	President's Emergency Plan for AIDS Relief
PMTCT	Prevention of mother-to-child transmission
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RR	Rate ratio
SD	Standard deviation
SMS	Short message service
STI	Sexually transmitted infection
SSA	Sub-Saharan Africa
UGDH	Uasin Gishu District Hospital
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

1 BACKGROUND

1.1 HIV OVERVIEW

Human immunodeficiency virus (HIV) was introduced to humans in sub-Saharan Africa (SSA) in the early 20th century and has been a significant public health concern since the first cases of acquired immunodeficiency syndrome (AIDS) were reported in the USA in 1981 (1, 2). The spread of HIV has led to a worldwide pandemic, with an estimated 37.7 million people living with HIV, 1.5 million people newly infected, and 680,000 people who died from AIDS in 2020 (3). Many countries in SSA have been particularly affected by the HIV pandemic, with SSA accounting for 67% of people living with HIV (3) and 60% of all new HIV infections worldwide in 2020 (4). Of new HIV infections in SSA in 2020, 63% were among women or girls, and women of reproductive age (15-49 years) were most at risk of acquiring HIV (4).

With the discovery of effective antiretroviral therapy (ART) in the mid-1990s, HIV has shifted from a disease with a very high mortality to a manageable chronic condition (5). With the inception of economic initiatives such as the Global Fund (6) and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) (7), ART coverage has been scaled up since the early 2000s in most of the low- and middle-income countries in SSA with a high HIV-prevalence (6-9). This has led to a worldwide decrease of people dying from AIDS as well as fewer people newly infected with HIV (4), the latter due to a greatly decreased risk of sexual HIV transmission from people on sustained ART (10-12). To further decrease HIV transmission and improve HIV health outcomes, the proportion of people living with HIV who are diagnosed and reached by treatment programmes must increase (4, 13). The Joint United Nations Programme on HIV/AIDS (UNAIDS) has set a 95-95-95 target to end the AIDS epidemic as a public health threat by 2030, meaning that 95% of all people living with HIV should (I) know their HIV serostatus, (II) receive sustained ART, and (III) achieve HIV viral suppression (13). At the end of 2020 an estimated 84% of people living with HIV worldwide knew their HIV status, 87% of those who were diagnosed were on treatment, and 90% of those on treatment were virally suppressed, although with large differences between regions and subpopulations (4). One important factor for achieving the 95-95-95 target is to retain people living with HIV in care to ensure their access and adherence to ART.

1.2 PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV

Mother-to-child transmission (MTCT) is the main cause of HIV infections in children and can occur during pregnancy, delivery, and breastfeeding (14). There has been a decline of MTCT during the last decades (Figure 1), mainly due to increased global access to ART (14). However, despite this decline, an estimated 150,000 children (aged 0-14 years) worldwide were newly infected with HIV in 2020 (8).

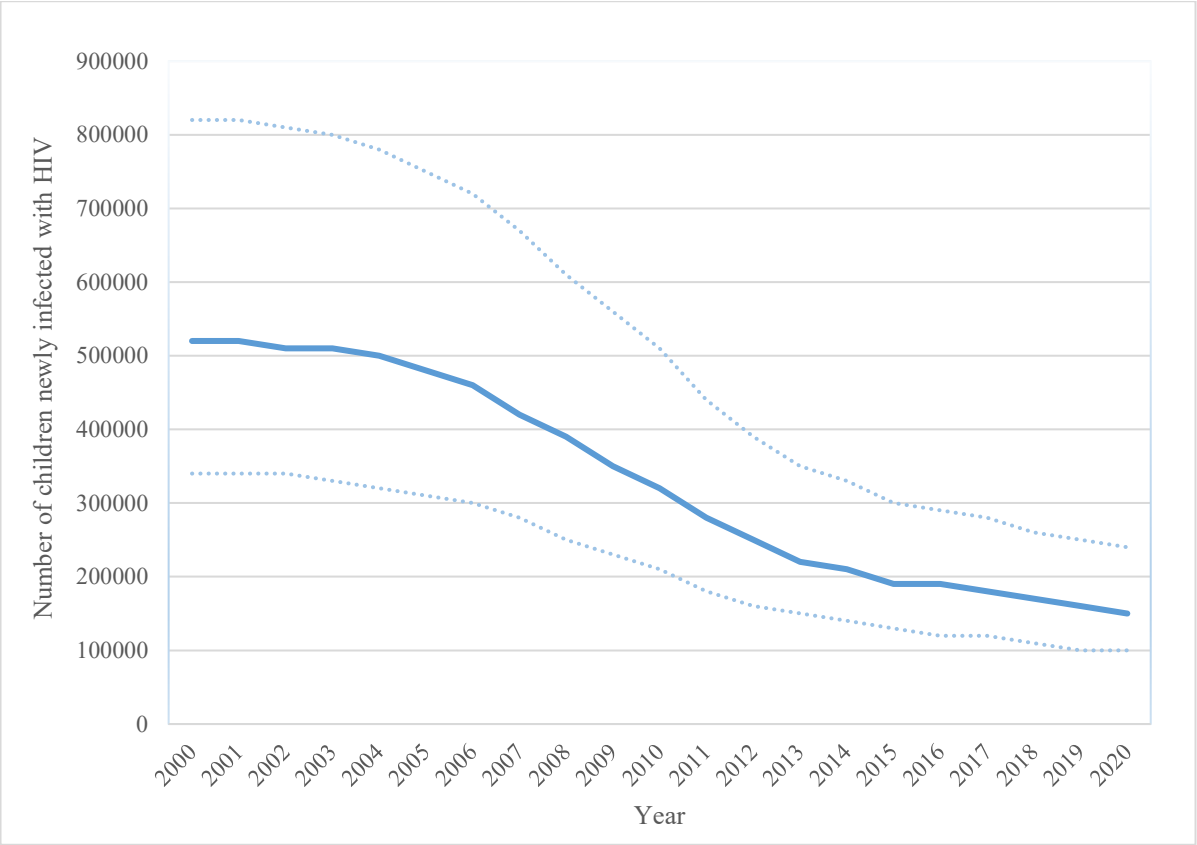

Figure 1. Estimated annual number of children (0-14 years) newly infected with HIV worldwide 2000-2020.

Source of data: Joint United Nations Programme on HIV/AIDS.

Children constitute a vulnerable group who are less likely to access sustained ART, and only 40% of children living with HIV worldwide were estimated to be virally suppressed in 2020 compared to 67% of adults living with HIV (4). Children accounted for 5% of people living with HIV but comprised 15% of AIDS-related deaths worldwide in 2020, due to insufficient access to effective ART (8). Without ART or other interventions, HIV is transmitted to 15-45% of infants born to women living with HIV (14). To reduce MTCT rates, pregnant women living with HIV have been treated with ART and their newborn infants have received antiretroviral prophylaxis at delivery since the mid-1990s (14). A meta-analysis from 1999 of 8,533 mother-infant-pairs from 15 prospective cohort studies reported that Caesarean section reduced the MTCT risk compared to vaginal delivery (15). However, if women are virally suppressed, vaginal delivery is currently recommended to most pregnant women living with HIV, as it does not increase the risk of MTCT compared to Caesarean section (16).

In 2012, the World Health Organization (WHO) introduced the prevention of mother-to-child transmission (PMTCT) of HIV Option B+ guidelines, recommending continued lifelong ART for all pregnant women living with HIV (17). Implementation of PMTCT Option B+ has led to decreased MTCT of HIV in many HIV high prevalence countries in SSA (8). Figure 2 illustrates the WHO's PMTCT Option B+ treatment and testing cascade.

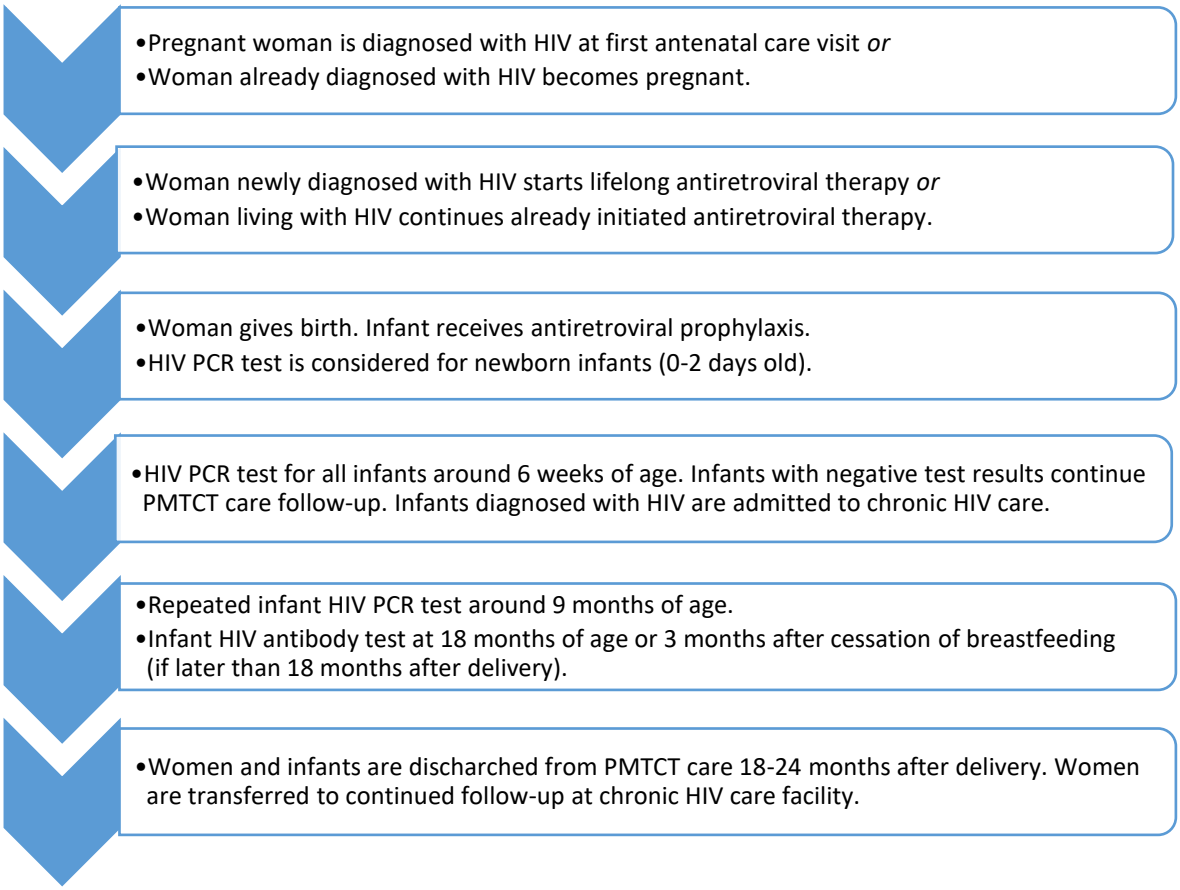

Figure 2. The World Health Organization's PMTCT Option B+ treatment and testing cascade.

PCR, Polymerase Chain Reaction; PMTCT, Prevention of mother-to-child transmission of HIV.

Early infant diagnosis (EID) of HIV and an early start of ART is important to reduce mortality among infants infected with HIV (18, 19). According to the WHO's PMTCT guidelines, a polymerase chain reaction (PCR) HIV test should be considered for HIV-exposed infants (HEIs) at birth, and it is strongly recommended around six weeks of age (19). In low- and middle-income settings with limited access to safe substitution feeding, mothers living with HIV are instructed to exclusively breastfeed their infants for six months (19). The WHO also recommends a repeated HIV PCR test around nine months of age (19) and a final antibody test around 18 months of age, or three months after the cessation of breastfeeding (if later), to confirm the HEI's serostatus (19) when maternal HIV antibodies no longer are detectable (19).

1.2.1 Retention in PMTCT care

Despite the WHO's recommendation of lifelong ART, many women have insufficient adherence to ART and attending scheduled clinic appointments, which contributes to treatment failures and increased MTCT rates (8, 20). A meta-analysis of 22 studies from SSA reported a pooled estimate of 69% being retained 24 months after initiating ART in PMTCT

Option B+ care, and retention rates decreased with time in follow-up (21). In many countries in SSA including Kenya, Mozambique, Zambia, and the United Republic of Tanzania, a substantial proportion of MTCT occurs after the early infant HIV testing at six weeks postpartum due to continued breastfeeding of infants without adequate maternal HIV suppression (8). An estimated 31,000 new infections in infants could have been averted in the 21 most HIV-inflicted priority countries in SSA if women on ART would have been retained in PMTCT care throughout pregnancy and breastfeeding in 2020 (8). In addition to increased MTCT, low ART adherence also leads to increased maternal morbidity and mortality (20), which also threatens their infants' health and survival (22, 23).

1.2.2 Barriers and facilitators to retention in PMTCT care

Several social, personal, logistical, HIV-related, and healthcare-related factors have been observed to be barriers to retention in PMTCT care including lower age (24-28) and education (24, 29) among women. To be newly diagnosed with HIV (30, 31) and to start ART on the day of the HIV diagnosis (26) may be associated with denial or not having accepted the need to take lifelong ART. Other barriers in low- and middle-income countries include difficulties to access the clinic due to long distance and time to reach the clinic (24), as well as cost of transportation (32), particularly in rural areas where women may have to prioritise between the economic interests of the family and the health of herself and her infant. Long waiting times at the clinic, limited clinic opening hours, or discriminatory or other negative treatment by healthcare workers are examples of healthcare-related barriers to retention in PMTCT care (33). On the other hand, counselling and education about HIV and ART, and participation in peer-support groups at the clinic or in the community, were suggested to be facilitators to improve engagement in PMTCT care and adherence to ART according to a majority of women in a case-control study from Malawi (24).

A 2015 systematic review of 47 studies among pregnant and postpartum women from 14 countries in SSA reported a pooled estimate of 67% who had disclosed their HIV serostatus to someone, and 64% to a partner (34). HIV-related stigma, discrimination, and concerns about involuntary HIV status disclosure are important barriers that can lead to difficulties accessing healthcare facilities due to fear of being recognized by family or friends (27, 35-40). Women who have not disclosed their HIV status to a partner may have to hide their ART medication or have difficulties visiting the clinic without raising their partner's suspicion (41). In addition, lack of partner support due to non-disclosure of HIV status has been cited as a major barrier to uptake of and retention in PMTCT Option B+ care (42, 43). HIV disclosure is also important to promote facility delivery (44, 45), early infant HIV testing (46), adherence to infant antiretroviral prophylaxis (47, 48), and infant feeding guidelines (49). Studies have observed that HIV status disclosure to a partner (50, 51), knowing the partner's HIV status (24), partner support (24), support from family, friends and other people living with HIV (52) are social facilitators that can improve retention in PMTCT care and ART adherence.

Qualitative studies from SSA suggest that many women in PMTCT care do not disclose their HIV status due to concerns of separation or divorce (41, 42, 53-55), emotional abuse (53-55), intimate partner violence (42, 53-56) and stigma in the family or community (54, 56). There is, however, evidence of decreasing HIV-related stigma in SSA (54, 57). The proportion of the Kenyan population reporting discriminatory attitudes toward people living with HIV decreased from 28% to 12% between 2009 to 2014 (57), and a 2017 mixed-method study from Uganda reported that the majority of women in PMTCT care felt that HIV-related stigma had decreased in their communities (54). In light of this evidence of changing attitudes towards people living with HIV in SSA, and the lack of previous quantitative studies in this research area, we identified a knowledge gap of the current prevalence of pregnant women's social and emotional barriers related to participation in PMTCT care. We also wanted to investigate how these social and emotional barriers were related to HIV status disclosure to partners and relatives among women at enrolment in PMTCT Option B+ care, where previous data were lacking.

1.3 KENYA

Kenya, a lower middle-income country (58) in east Africa, has a population of 47.6 million according to the 2019 census (59). The Kenyan economy predominantly relies on agriculture and had an average growth rate of 5.7% per year between 2015-2019, which was one of the fastest in SSA (58). In 2014, shortly before the start of the WelTel PMTCT trial included in this thesis, 86% of Kenyan households overall and 80% of rural households were in possession of a mobile phone (60). Mobile phone access has continued to increase and 98% of Kenyans had a mobile connection in 2019 (61). By the start of our trial, 67% of women of reproductive age (15-49 years old) had completed at least eight years of primary schooling, 88% were literate, and 61% were employed according to a nationwide survey (60).

1.3.1 Reproductive and maternal health in Kenya

The fertility rate in Kenya has fallen during the last decades, and was 3.9 births per woman by the start of our trial (60). Childbearing often starts around 20 years of age (60). In 2014, most of Kenyan women who previously had given birth had attended antenatal care (ANC) during pregnancy (96%) to meet a skilled provider (a nurse, midwife, or doctor), 61% delivered in a healthcare facility, and 62% were assisted at delivery by a skilled provider (60). Rural residence, lower educational level and lower household income were associated with higher fertility rate, lower age at first delivery, not receiving ANC from a skilled provider, not being delivered at a health facility, or by a skilled health provider (60). Most pregnant women in Kenya present quite late in the pregnancy to ANC, with a median gestational age at the first ANC visit of 5.4 months (60). The median time of exclusive breastfeeding was 4.3 months, whereas non-exclusive breastfeeding continued for a median of 21.3 months in 2014 (60). Mortality for children under five years of age has decreased over time in Kenya, and

this decline continued during the course of our trial from 5.2% to 4.2% between 2014 and 2020 (60, 62).

Pregnant women with previously negative or unknown HIV status should be HIV tested at the first ANC visit according to Kenyan guidelines (63). If the test is negative, a retest should be performed in the third trimester, at delivery, at six weeks and six months postpartum (63). In 2014, 20% of women of reproductive age were not aware that sexual transmission of HIV could be prevented by condom use and almost a quarter (24%) of pregnant women were not aware that the risk of MTCT could be reduced by taking medication during pregnancy (60).

1.3.2 HIV and PMTCT care in Kenya

HIV and MTCT are significant public health concerns in Kenya, where 1.4 million people were living with HIV in 2020 (64). In addition, an estimated 5,200 children and 28,000 adults were newly infected with HIV in 2020 (64). The HIV prevalence among adults of reproductive age was 4.2%, and women accounted for 64% of the adult population living with HIV in Kenya in 2020 (64). The HIV prevalence varies greatly by geographic region, from 0.1% in the north-eastern county Wajir to more than 20% in the western counties Siaya and Homa Bay (65). Kenya started implementing the WHO's PMTCT Option B+ guidelines in 2013 (66) and pregnant women's access to ART has increased in recent years from 55% in 2010 to 94% in 2020 (67) (Figure 3).

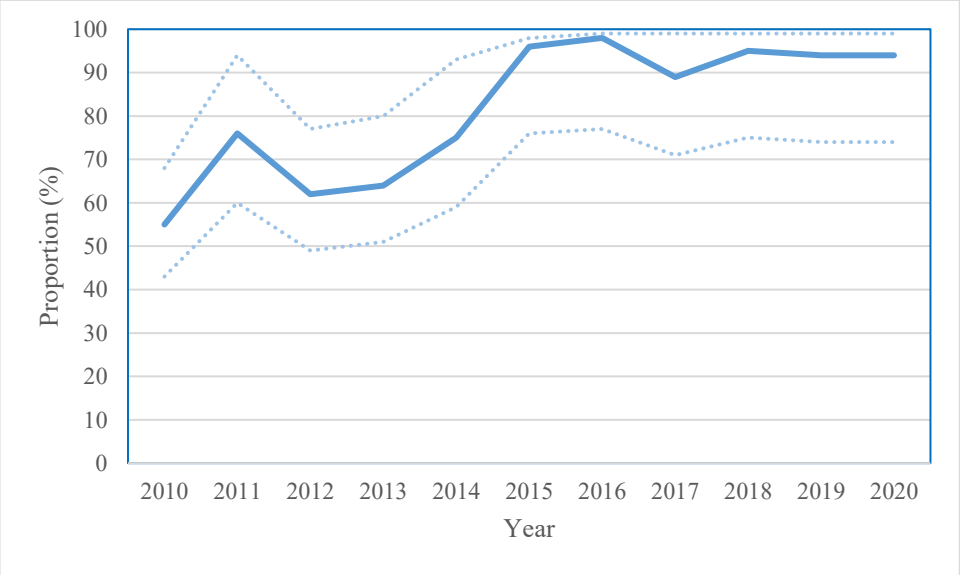

Figure 3. Estimated proportion of pregnant women living with HIV in Kenya who received antiretroviral therapy for prevention of mother-to-child transmission 2010-2020.

Source of data: Joint United Nations Programme on HIV/AIDS.

Poor adherence to ART and retention in care has been a challenge to outcomes of HIV and PMTCT care in Kenya. A quarter of 546 people enrolled in HIV care had poor ART adherence and approximately a third had viral failure (>1,000 copies/ml) in a 2015 multicentre study (68). As previously mentioned, MTCT during the postpartum period is a problem in Kenya as demonstrated by the final MTCT rate in Figure 4. The six-week postpartum transmission rate in Kenya was 5%, and the final MTCT rate was 10% in 2020 (8). This is a significant improvement compared to the pre-PMTCT Option B+ final MTCT rate of >20% in 2010 (69), but Kenya is still far from the national target of a 3% final MTCT rate by the end of 2021 to eventually achieve elimination of mother-to-child transmission (EMTCT) (70).

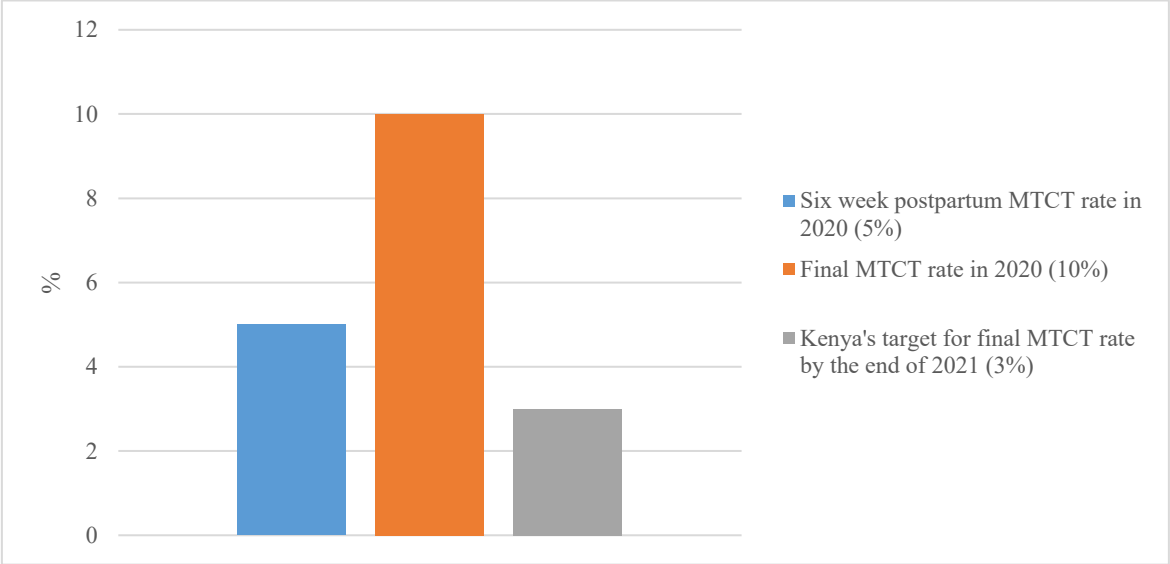

Figure 4. Mother-to-child transmission (MTCT) of HIV in Kenya 2020 and national target for 2021.

Sources of data: Joint United Nations Programme on HIV/AIDS and Ministry of Health, Kenya.

1.4 MOBILE HEALTH

Increased access to mobile phones and the evolution of mobile phone technology has opened up the field of mobile health (mHealth) to use text messaging, voice calls, smartphone apps, video, etc. to promote health by behavioural change, enhancing medical education, and facilitating laboratory diagnostics, health reporting, and surveillance (71). Studies from high-income settings have reported that mHealth can be used to promote healthier behaviours including smoking cessation and decreasing alcohol intake (71, 72). mHealth has also been reported to improve drug adherence and clinic attendance for different medical conditions including hypertension (73), obesity (74), and cystic fibrosis (75). Text-messaging reminders were observed to reduce non-attendance to scheduled appointments among patients in various medical disciplines in 2005 (76).

Falling prices have led to a very rapid increase of mobile phone access among men and women in low- and middle-income countries in SSA (77), which has created an opportunity to use mHealth in resource-limited settings where access to healthcare has been restricted by lacking infrastructure, human resources, and physical resources (71). In 2019, 80% of women in low- and middle-income countries owned a mobile phone, representing an increase of 250 million more women with mobile phone access compared to 2014 (78). mHealth interventions have been reported to improve outcomes of antenatal and postnatal care for women in low- and middle-income countries according to a systematic review of 30 studies (79). In addition, mHealth interventions have been reported to improve maternal health, adherence to treatment, HIV prevention, and attendance to scheduled appointments in resource-limited settings (79-81).

1.4.1 Mobile health to improve outcomes in HIV care

Several studies in SSA have tested whether mobile text messaging or voice calls improve uptake of HIV services, attendance to scheduled appointments, ART adherence, and retention in care. A prospective cohort intervention study of 176 people living with HIV in Uganda reported that 79% of those who missed a scheduled appointment showed up shortly at the clinic (within 2.2 days) if they received a reminding voice call (82). Before the 2015 start-up of the WelTel PMTCT trial that this thesis is based on, another randomised controlled trial (RCT) of 431 people living with HIV in Kenya had reported that weekly text messaging improved ART adherence and decreased treatment interruptions during 48 weeks of follow-up (83). A 2012 Cochrane review concluded that weekly mobile phone text messaging enhanced ART adherence and HIV viral load suppression, and that policymakers should consider implementing text-messaging interventions to promote ART adherence (84). In contrast, a 2014 RCT from India reported no effect of text messaging on viral suppression or ART adherence during a two-year follow-up of 631 people living with HIV (85).

Two RCTs have investigated whether the weekly interactive (WelTel) text-messaging intervention studied in this thesis could improve outcomes for people enrolled in general HIV care in Kenya (86, 87). A 2010 RCTs of 538 people living with HIV reported that the WelTel intervention improved HIV viral load suppression and self-reported ART adherence during the first year of HIV care (86). An in-depth analysis of the trial reported that the main reason for sending text message responses indicating a problem were health-related issues, and lower age and rural residence were associated with more reported problems (88). Lower education and study site were factors associated with participants' non-adherence to sending weekly text-messaging responses (88). A later 2018 RCT of 700 people living with HIV reported no effect of the WelTel intervention on retention during the first year in HIV care (87). A qualitative study did, however, suggest that the interactive WelTel intervention could improve early identification and timely solving of problems including poverty, depression, and HIV-related stigma among people enrolled in general HIV care (89). In addition to those problems, women enrolled in PMTCT care may also experience problems related to the

pregnancy, delivery, and the care of a newborn infant which may require timely solving, support, and counselling (21, 90). We therefore identified a knowledge gap of the WelTel intervention effect on outcomes of PMTCT care, since none of the previous WelTel RCTs had included pregnant and postpartum women living with HIV (86, 87).

1.4.2 Mobile health to improve outcomes in PMTCT care

Several studies have investigated the effect of various mHealth interventions including voice calls (91), need-based counsellor-delivered phone calls (92), web-based tools to improve communication (93) and combined voice call and text-messaging intervention (94) with promising results on PMTCT outcomes. An RCT of 150 pregnant women in Kenya reported that fortnightly mobile phone calls increased self-reported adherence to give their infants antiretroviral prophylaxis, and increased retention in PMTCT care at six and ten weeks postpartum (91). Another RCT including 404 women reported that counsellor-delivered phone calls increased retention in PMTCT care at six and fourteen weeks postpartum (92). An RCT of 895 women in Kenya reported that a web-based intervention to link providers of EID HIV testing to laboratory technicians and mothers improved EID HIV testing, especially in medium- and low-volume hospitals, compared to standard care (93). A four-armed RCT of 242 HEIs and children living with HIV in Cameroon reported that text messaging, voice calls, and text messaging and voice calls combined all significantly improved attendance to scheduled appointments compared to no intervention (94). Text messaging plus voice calls was the most effective combination to improve attendance to scheduled appointments (94).

1.4.3 Text-messaging interventions in PMTCT care

There have been several studies that have reported significant effects of text-messaging interventions on outcomes in PMTCT care (95-97). An RCT of 388 pregnant women conducted before the implementation of PMTCT Option B+ in Kenya reported that text messaging improved mother-infant-pairs returning for an EID HIV test by eight weeks postpartum (95). Another RCT of 552 pregnant women from Mozambique reported that a series of text-messaging reminders significantly improved institutional delivery and EID HIV testing by eight weeks postpartum (96). In line with these results, an intervention study conducted in South Africa reported that EID HIV testing significantly increased after the implementation of a text message intervention, where women-infant-pairs of similar eligibility enrolled in PMTCT care prior to the implementation of the intervention served as a control group (97). Other text-messaging intervention trials have not observed improvements of clinical PMTCT outcomes (98-100). A cluster-RCT of 2,472 pregnant women conducted in Kenya reported no effect of text messaging on retention in early postpartum care among women, and there was no effect on EID HIV testing within eight weeks postpartum (98). Another multicentre RCT of 550 women conducted in Kenya (99) and a non-randomised

retrospective interventional study conducted in South Africa (100) reported no effects of text messaging on EID HIV testing.

At the start of the WelTel PMTCT trial that this thesis is based on, none of the previous text-messaging intervention studies had investigated the effect on retention until the end of the PMTCT care period, nor on women's postpartum linkage to chronic HIV care which is highly relevant in the PMTCT Option B+ era. In addition to this observed knowledge gap, none of the previous RCTs had investigated an intervention where women in PMTCT care were contacted if they did not respond to the text messages. There was also a lack of previous data on the use of and adherence to an interactive text-messaging intervention among women in PMTCT care, which is important to investigate when evaluating the impact of a text-messaging intervention strategy (101).

2 RESEARCH AIMS

2.1 AIM

To increase knowledge of the effect of an interactive text-messaging intervention on retention in PMTCT care, and to shed light on pregnant women's HIV status disclosure and their social and emotional barriers to participate in PMTCT care in Kenya.

2.2 SPECIFIC OBJECTIVES

1. To investigate how social concerns related to participation in PMTCT care are associated with HIV status disclosure to partners and relatives among pregnant women living with HIV (paper I).

2. To investigate the effect of a weekly, interactive text-messaging intervention on the uptake of early infant HIV testing (paper II).

3. To investigate the effect of a weekly, interactive text-messaging intervention on 18-months postpartum retention in PMTCT care (paper III).

4. To investigate the effect of a weekly, interactive text-messaging intervention on the proportion of women who delivered at a healthcare facility, retention in PMTCT care between six and 12 months postpartum, women's postpartum linkage to chronic HIV care, and time in care up to 30 months from enrolment (paper III).

5. To investigate how women in PMTCT care used, adhered to, and evaluated a weekly, interactive text-messaging intervention (paper IV).

6. To investigate how the use and adherence to respond to weekly text messages were associated with sociodemographic or health characteristics among women in PMTCT care (paper IV).

3 MATERIALS AND METHODS

3.1 STUDY SETTING

WelTel PMTCT was an RCT that was carried out at six clinics spread over a large area of the Rift Valley, Nyanza, and Western provinces of Kenya (Figure 5). The six government-run clinics are part of the Academic Model Providing Access to Healthcare (AMPATH) programme and are located in urban and rural areas in the agriculturally important Uasin Gishu, Trans-Nzoia, Kisumu and Busia counties. Three of the clinics (at the Moi Teaching and Referral Hospital (MTRH), Uasin Gishu District Hospital (UGDH), and Huruma Sub-County Hospital) are in Eldoret, the fifth most populated town in Kenya with 476,000 residents according to the 2019 population census. The Kitale County Referral Hospital is in the town Kitale with a population of 162,000 people according to the 2019 census, whereas the clinics located in Chulaimbo and Matayos are in rural areas. AMPATH is a partnership between the MTRH, the Moi University, the Kenyan Ministry of Health, and academic institutions in high-income countries led by the Indiana University in the United States (102).

The female adult HIV prevalence varied widely between the study sites from an estimated 5.5% in Uasin Gishu county to 17.4% in Kisumu county in 2017 (65). There were also sociodemographic and maternal health differences between the counties where the study sites are situated, with educational attainment ranging from 6.5 to 7.9 years, the literacy rate from 86% to 94%, the fertility rate from 3.6 to 5.4 children per woman, and the age at first childbirth from 18.8 to 20.3 years in 2014 (60).

During a significant part of the study period (in 2016 and 2017), there were national strikes among nurses and doctors in Kenya, which limited access to care in all hospitals in the study setting. HIV and PMTCT care services were, however, mainly uninterrupted at the six clinics due to the work of AMPATH clinical officers and mentor mothers who did not strike. There was a limited access to hospital delivery services during a significant part of 2017. There were also reports of fewer PMTCT care visits than usual as well as missed PMTCT care appointments because not all patients were aware that HIV and PMTCT care still could be accessed during the strike.

Participants were recruited between 25 June 2015 and 5 July 2016. Only five participants were enrolled at the Matayos clinic due to late start of recruitment (in April 2016). Data was collected at baseline, during, and after follow-up of the participants. Follow-up concluded at 30 months postpartum on 26 July 2019. All data collection was due in September 2020.

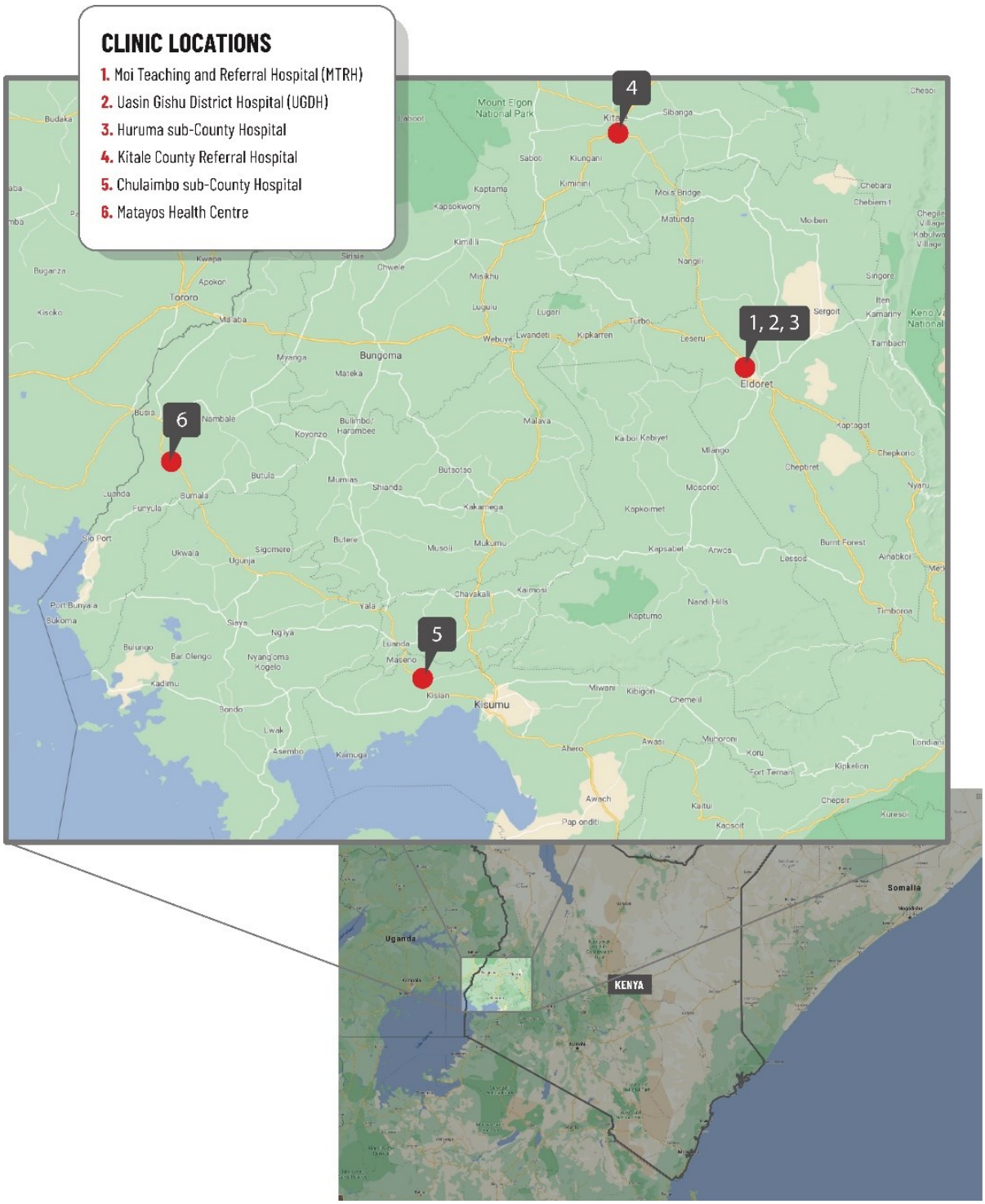

Figure 5. Location of the study sites in western Kenya.

3.2 STUDY POPULATION

Pregnant women living with HIV or newly diagnosed with HIV were invited to participate at their first ANC visit in the current pregnancy. To be eligible, women had to be 18 years or older, provide an informed consent, be a resident of the clinic catchment area, own or have access to a mobile phone, and be able to send text messages or have someone in close contact who could read and respond to text messages on their behalf. Women who were not willing

to be followed-up or planned to relocate within 24 months postpartum were excluded. The infants delivered by women enrolled in the trial were also included in trial follow-up.

3.3 STUDY DESIGN

3.3.1 Randomisation, allocation, and blinding

After a face-to-face interview in English or Swahili at enrolment, the participants were randomly assigned in a 1:1 allocation ratio to the intervention or control group. Randomisation was performed separately at each study site using individual, sealed, opaque envelopes. A computer-generated permuted-block randomisation scheme was generated by an independent statistician for each clinic separately, using block-sizes equal to four to ensure balance between the study groups. The randomisation sequence was generated by using the ralloc command in Stata. Due to the nature of the intervention, the trial was open-label and unmasked to the participants and the healthcare workers who responded to the participants' texts. The laboratory staff, collectors of data from patient registers and medical files, and researchers were blinded until data cleaning was complete and the database was unlocked.

3.3.2 The WelTel Intervention

The weekly interactive text-messaging (WelTel) intervention is described in Figure 6. Upon allocation to the intervention group, the participants' mobile phone numbers were registered in a digital platform. The participant thereafter received automatically generated weekly text messages from a generic number asking "Mambo?" (Swahili for "How are you?") every Monday morning until 24 months postpartum. The participants were instructed to respond that they were "okay" ("sawa" in Swahili) or that they had a "problem" ("shida" in Swahili). The text message responses were automatically registered in the digital WelTel platform. In addition, the problem responses were automatically sent to a mobile phone at the clinics. A research coordinator monitored the digital platform and prepared weekly lists of participants who had not responded within 48 hours, which were forwarded to the clinics by paper or a text message. A healthcare worker (e.g., a nurse or a mentor mother) called those who had reported a problem and those who had not responded to provide assistance and counselling, and to refer them to the clinic if needed.

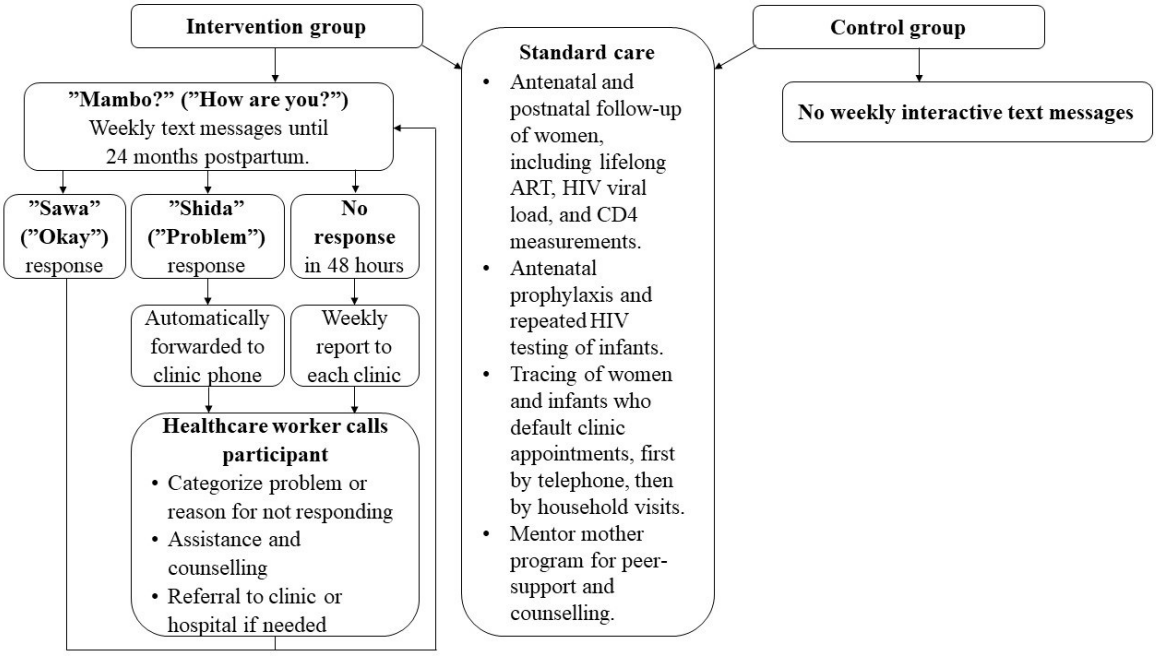

Figure 6. The WelTel intervention and prevention of mother-to-child transmission of HIV standard care.

ART, Antiretroviral therapy.

Healthcare workers also categorized problems during the follow-up phone calls and they registered the problems in a paper log in the categories: (1) health related, (2) social or domestic, (3) economic or financial, (4) psychological, or (5) need of information. They also entered the participants open-ended reasons for not responding to a text message in a paper log. The text messaging continued as planned if a participant transferred care to another clinic or was lost to follow-up, but it was stopped in case of a miscarriage, stillbirth, infant death, maternal death, or withdrawal. At 24 months postpartum, a follow-up interview was carried out with the participants who were still engaged in PMTCT care, to evaluate their opinions about the intervention as well as the perceived benefits and barriers related to interactive text messaging.

3.3.3 Standard care

Participants in both the intervention and control group received standard PMTCT Option B+ care (21) and antiretroviral prophylaxis for the infant, which was offered free of charge according to the prevailing guidelines. Standard care included check-up appointments and monitoring of HIV viral load and CD4 count. It also included counselling related to HIV, adherence to ART, and infant feeding guidelines as well as screening for sexually transmitted infections, intimate partner violence, and tuberculosis. The Kenyan PMTCT guidelines used in clinical practice during the main part of the study period were released in 2016 (63). The guidelines recommended tenofovir disoproxil fumarate + lamivudine + efavirenz as the first

line ART regimen (63). According to the guidelines, an HIV ribonucleic acid (RNA) viral load test should follow six months after initiation of ART, and in case of treatment failure (HIV RNA viral load >1,000 copies/ml) the testing should be repeated every third month with intensified adherence counselling (63). If a second test showed HIV RNA >1,000 copies/ml, switching to an alternative second line ART regimen was recommended (63). The guidelines recommended vaginal delivery under the care of a skilled birth attendant among virally suppressed women, but for women with HIV RNA >1,000 copies/ml or with unknown HIV RNA level at delivery, an elective Caesarean section was recommended instead (if feasible) (63).

Women were recommended to exclusively breastfeed their infants for six months (63), and continued breastfeeding with complementary feeding was recommended until the infant was one year old (63). Infant antiretroviral prophylaxis with nevirapine + zidovudine was recommended for six weeks postpartum followed by single therapy with nevirapine for an additional minimum of six weeks, after which the prophylaxis could be discontinued if maternal viral suppression was confirmed, according to the 2016 guidelines (63). Infants were HIV tested due to the prevailing guidelines (63, 66), which were updated during the course of the trial. Before the release of the 2016 guidelines (63), infants were tested with a PCR test at six weeks of age, and antibody tests at nine months and 18 months of age. After the release of the 2016 guidelines (63), infants were tested with PCR tests at six weeks, six months, and 12 months of age. They were also tested with an antibody test at 18 months of age, and a repeated antibody test was recommended six weeks after the cessation of breastfeeding (63). In addition, at birth HIV PCR testing was piloted at some of the clinics during parts of the study period. Infants who were diagnosed with HIV were referred to a chronic HIV care clinic.

According to standard PMTCT care at the clinics, pregnant women were scheduled for an appointment two weeks after the first ANC visit, which was followed by monthly appointments during pregnancy and the first year postpartum. However, women who were ART adherent and had a suppressed viral load were scheduled for follow-up visits every third month. One year postpartum, women were scheduled to return to the clinic every third month for routine follow-up visits. Staff at the clinics called women who defaulted scheduled appointments by telephone, and physically tracked those who did not return to the clinic within one week of a missed appointment (103, 104). During the trial from 2015 to 2017, PMTCT care became integrated with general antenatal and postnatal care for people not living with HIV to reduce stigma associated with visiting clinics exclusively designated for people living with HIV (70, 105). The clinics had also implemented a mentor mother programme for peer-support and counselling of pregnant women living with HIV (70). At 18 to 24 months postpartum, women were referred to a comprehensive care clinic for continued chronic HIV care. Women were immediately referred to the comprehensive care clinic in case of a miscarriage, stillbirth, or infant death.

3.4 OVERVIEW OF PAPERS

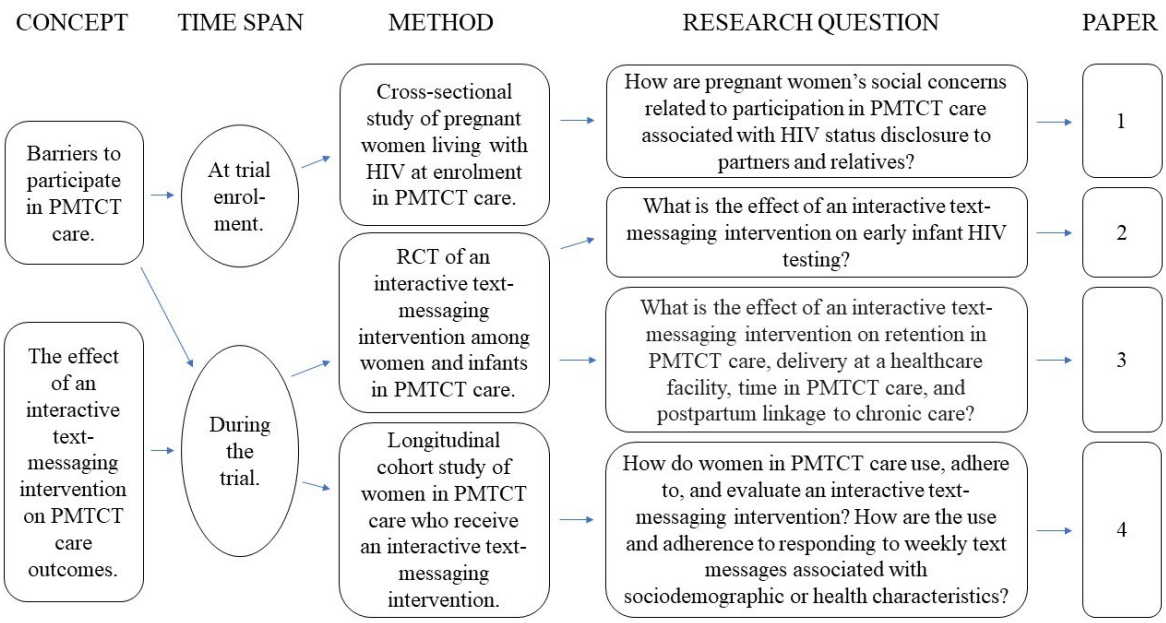

Figure 7. Overview of papers.

PMTCT, Prevention of mother-to-child transmission; RCT, Randomised controlled trial.

3.4.1 Paper I

This is a cross-sectional study based on data collected at participants' enrolment in the WelTel PMTCT trial. The study included 437 pregnant women living with HIV who were enrolled at their first ANC visit in the current pregnancy at the ANC clinics of the Huruma Sub-County Hospital, the Kitale County Referral Hospital, the MTRH, and the UGDH. At these four clinics, women were interviewed at study enrolment about social concerns related to participation in PMTCT care. In addition, they were also interviewed about HIV testing, time of HIV diagnosis, HIV status disclosure, barriers to accessing healthcare, and mobile phone access. Women diagnosed with HIV the day they were enrolled in the WelTel PMTCT trial were excluded from this cross-sectional study due to lack of opportunity of HIV status disclosure to a partner or a relative.

Outcomes: Self-reported HIV status disclosure (to a partner/a relative/another person). Self-reported concern of involuntary HIV status disclosure (related to participation in HIV care or taking ART). Self-reported concern that attending PMTCT visits or taking ART would lead to participants (I) being a burden or source of concern for others; (II) losing the respect of family or community; (III) being isolated or lacking support from family or friends; (IV) being teased or insulted; (V) being separated from a partner; (VI) having a conflict with a

partner; (VII) losing customers or a job; (VIII) being a victim of intimate partner violence; (IX) having a child taken away; (X) having property taken away.

Data source: Data collected face-to-face using an interviewer-administered questionnaire at enrolment in PMTCT care.

Statistical analysis: Multivariable-adjusted logistic regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of the associations between social concerns and HIV status disclosure to a partner or a relative. Based on previous literature on HIV status disclosure, ORs were adjusted for age (106, 107), educational level (108), marital- and cohabitation status (109-112), working status (113), time since HIV diagnosis (106), living with relatives (114) and economic situation (53, 106, 110) of the participants. A variable was excluded from the logistic regression model if a response alternative was reported by <10 women (excluding concerns about intimate partner violence, a child taken away, and property taken away). We also investigated whether clinic of enrolment attenuated ORs and 95% CIs of the multivariable-adjusted analyses. SPSS (IBM Corp. Released in 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) was used for data analysis.

3.4.2 Paper II and III

Papers II and III are based on results from the two-armed, parallel-group, randomised, open-label trial where 600 pregnant women living with HIV were enrolled at all six study sites and followed-up until 30 months postpartum. Follow-up also included infants born to the participants. However, only the infants resulting from the pregnancy that made women eligible for the trial were followed up. Paper II reported the effect of the WelTel intervention on uptake of early infant HIV testing. Paper III reported the effect of the WelTel intervention on retention in PMTCT care at 18 months postpartum (primary outcome of the trial).

Outcomes in paper II: Early infant HIV testing by eight weeks of age. Early infant HIV testing between four to eight weeks of age. Infants infected with HIV by eight weeks of age.

Outcomes in paper III: Retention in PMTCT care between six to 12 months postpartum. Retention in PMTCT care at 18 months postpartum. Women's postpartum linkage to chronic HIV care. Time in care up to 30 months from enrolment. Delivery at a healthcare facility. Infants infected with HIV during trial follow-up.

Data sources: Data was extracted from medical records, patient registers, and the National AIDS and STI Control Programme (NASCOP) register.

Statistical analysis: The primary analysis of the intervention effect on primary and secondary trial outcomes in papers II and III were intention-to-treat, including all participants randomly assigned, with Poisson regression analyses with robust standard errors to estimate rate ratios (RRs) and 95% CIs. We also did sensitivity analyses with adjustment for age, time from HIV diagnosis to enrolment, and site. Additional sensitivity analyses excluded participants with a

miscarriage, stillbirth, death of the infant or mother, or transfer to another clinic. Hazard ratios for dropout from care were estimated by Cox models. Poisson regression with robust standard errors was used to assess the interaction effect of the intervention across subgroups. StataCorp. 2011 and 2017. *Stata Statistical Software: Release 12 and 15*. College Station, TX: StataCorp LP, and StataCorp LLC were used for data analyses.

3.4.3 Paper IV

A longitudinal cohort study nested within the WelTel PMTCT trial of the 299 pregnant and postpartum women living with HIV randomly allocated to the trial intervention group at the six study sites.

Outcomes: Text-messaging outcomes included responses to messages ("okay" or "problem") and non-responses. Follow-up phone call outcomes included participants' problems categorized by healthcare workers, and reasons for not responding to text messages. Follow-up interview outcomes included questions of whether the intervention had been helpful, if participants wanted the text-messaging programme to continue, and questions of the greatest perceived benefits and barriers related to the weekly text message communication.

Data sources: Data of text-messaging outcomes were extracted from the WelTel platform. Follow-up phone call outcomes were extracted from paper logs used by healthcare workers. Follow-up interview data were collected face-to-face using an interviewer-administered questionnaire at 24 months postpartum.

Statistical analysis: Multivariable-adjusted logistic regression analyses were used to estimate ORs and 95% CIs of the association between baseline characteristics and (I) reporting a problem at least once, and (II) responding to <50% of the text messages received. Our count data for non-responses to text messages was overdispersed, and to assess the association between the number of non-responses and baseline characteristics we used negative binomial regression to estimate RRs and 95% CIs. Based on previous literature, ORs and RRs were adjusted for age (24, 25, 88), education (24, 29), being married or living with a partner (24), time since HIV diagnosis (30), HIV status disclosure (50), travel time to clinic (24), phone used in the study (88), and clinic of enrolment (33). ORs were also adjusted for the total number of text messages received in the study. RRs in the negative binomial regression analysis also included an offset for the log of the total number of text messages received. StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC was used for data analyses.

3.5 ETHICAL CONSIDERATIONS

Ethical approval was obtained from the Institutional Research and Ethics Committee at the Moi Teaching and Referral Hospital (FAN: IREC1292) and was renewed on an annual basis. Ethical approval was also obtained from the Regional Ethics Committee, Stockholm, Sweden (2018/742-31/1). The Swedish and Kenyan ethical approvals, including amendments, cover all four papers of this thesis. Informed consent was sought, verbally and in writing, from all participants enrolled in the WelTel PMTCT trial. Illiterate participants consented by thumb print in the presence of a witness who signed the form. All participants were informed by a research assistant that participation in the trial was voluntary, and that withdraw from the trial had no effect on them, their care, and the treatment provided to them. To ensure that all participants were properly informed prior to study enrolment, the informed consent form was provided to the participants in English or Swahili (depending on language preference) and the participants had opportunity to ask questions before signing the form. Extensive efforts were made to ensure participants' confidentiality, including keeping all study documents off-site and stored in locked filing cabinets, or password-protected with limited access in case of digital data. The risk of breach of confidentiality from the text-messaging intervention was minimised by the non-HIV-related content of the text messages. The number from where the text messages originated was not presented on the participants' mobile phone unless they actively installed a specific "true caller" software. All data entered into datasets and used for data analyses were deidentified and coded with a study id-number for each participant. To minimise the risk of study participants presenting late to healthcare in case of an urgent medical condition, the participants were carefully informed at trial enrolment that text messaging should not be used to contact their healthcare facility in case of a medical emergency. They were instead instructed to use the ordinary channels to contact the clinic for urgent medical conditions.

3.6 MY ROLE IN THE CONSTITUENT STUDIES AND PAPERS

I became involved in the WelTel PMTCT project in 2015. I first visited the study facilities in Kenya in September 2015 to meet the research team and to plan for my participation in the project and for my doctoral education. After my admission to doctoral education in 2016, I wrote the Swedish ethical application together with Katrine Chamorro de Angeles, one of four PhD students in the WelTel PMTCT project. I was responsible for cleaning and management of the baseline data that was collected at trial enrolment. Together with my supervisors, I drafted the design and hypothesis of the cross-sectional study described in paper I. I did the statistical analysis, drafted the first version of the manuscript, and submitted the manuscript for publication. I presented the main results of paper I as a poster at the HIV & Hepatitis Conference in Stockholm in 2019.

I have visited the study facilities in Kenya several times to follow-up on questions related to data collection of relevance for my thesis. In collaboration with the Kenyan study

coordinator Eunice Kaguiri, I performed checks and validations to ensure the quality of the data collected from different data sources by Kenyan research assistants. I was also involved in the decision-making on which data sources to use for extraction of data for papers II and III. I was involved in the design of the tools that were used for collection of data for the RCT primary and secondary endpoints (papers II and III). I participated together with the other PhD students and the primary investigators of the project (Professor Anna Mia Ekström and Professor Edwin Were) in updating the follow-up questionnaire used for face-to-face interviews by the local research assistants. I helped design the database used for entry of the data collected in the RCT (papers II and III). I also participated in the decision-making, design, and writing of the final statistical analysis plan used for data analyses together with the other Swedish and Kenyan researchers, and I took part in the process of finally defining some of the outcomes that required modification during the course of the trial. I wrote the section in the statistical analysis plan related to paper II. I formed the study hypothesis of paper II together with my supervisors, and I cleaned and analysed the data used in paper II. I drafted the manuscript and submitted it for publication. I took part in the data cleaning and data analysis related to paper III together with the co-first author Mia van der Kop. Mia and I drafted the manuscript of paper III and I have submitted it for publication. I also took part in decisions about the study design of paper IV after forming the hypothesis together with study coordinator Eunice Kaguiri and my supervisors. I cleaned and analysed the data and drafted the manuscript of paper IV.

4 RESULTS

4.1 PAPER I: SOCIAL CONCERNS RELATED TO HIV STATUS DISCLOSURE AND PARTICIPATION IN PMTCT OF HIV CARE

The characteristics of the 437 pregnant women in this cross-sectional study are presented in Table 1. Four out of five participants were married or living with a partner, and four out of five had been diagnosed with HIV six months or more before enrolment.

Table 1. Characteristics of pregnant women included in paper I (n=437).

Characteristic	**n (%)**
Age (years)	
18-24	84 (19.2)
25-29	122 (27.9)
30-34	123 (28.1)
35-44	108 (24.7)
Education	
Primary schooling or less	195 (44.6)
Secondary schooling	166 (38.0)
Higher education	76 (17.4)
Married or living with a partner	355 (81.2)
Living with relatives	97 (22.2)
Working outside the household	179 (41.0)
Economic responsibility	
Only for herself	247 (56.5)
For more people than herself	190 (43.5)
Time since HIV diagnosis	
<6 months	89 (20.4)
≥6 months	348 (79.6)

4.1.1 HIV status disclosure and social concerns

At enrolment, 202 women (46.2%) had disclosed their HIV status to a relative. Among the 355 women who were married or living with a partner, 284 (80.0%) had disclosed to a partner. In total, 34 (7.8%) had disclosed to another person. The most reported concern was involuntary HIV status disclosure (21.5%). This was followed by concern that attending PMTCT visits or taking ART would lead to them being a burden or source of concern for others (16.0%), losing respect of family or community (11.4%), isolation or lack of support from family or friends (9.4%), teasing or insulting (8.5%), separation from partner (5.5%), conflict with partner (5.0%), losing customers or a job (4.6%), intimate partner violence (1.1%) , having a child taken away (0.7%), and property taken away (0.2%).

4.1.2 Factors associated with HIV status disclosure

The associations between social concerns and HIV status disclosure are presented in Table 2. Concerns of separation from a partner (OR: 0.17; 95% CI: 0.05-0.57) and conflict with a partner (OR: 0.18; 95% CI: 0.05-0.67) were associated with significantly lower odds of HIV status disclosure to a partner. Participants aged 25-29 years (OR: 0.30; 95% CI: 0.11-0.81), 30-34 years (OR: 0.30; 95% CI: 0.11-0.86) and 35-44 years (OR: 0.15; 95% CI: 0.05-0.44) had significantly lower odds of HIV status disclosure to a partner compared to women aged 18-24 years.

Women with concerns of isolation or lack of support from family or friends had lower odds of HIV status disclosure to a partner (OR: 0.33; 95% CI: 0.12-0.85) and a relative (OR: 0.37; 95% CI: 0.16-0.85). Participants who had been diagnosed with HIV less than six months before enrolment had lower odds of HIV status disclosure to a partner (OR: 0.19; 95% CI: 0.09-0.39) and a relative (OR: 0.20; 95% CI: 0.10-0.39) compared to participants diagnosed with HIV six months or more before enrolment. In addition, participants who were married or living with a partner had lower odds of HIV status disclosure to a relative (OR: 0.35; 95% CI: 0.19-0.64).

Table 2. Social concerns and association with HIV status disclosure (n=423).

Disclosure of HIV status to:	**%**	**Partner[a] OR (95% CI)**	**Relative[b] OR (95% CI)**
Concern that attending PMTCT visits or taking ART would lead to:			
Involuntary HIV status disclosure[c]			
Yes	21.5	0.75 (0.39-1.44)	1.02 (0.60-1.71)
Uncertain	3.8	0.62 (0.14-2.70)	1.69 (0.53-5.41)
No	74.7	Reference	Reference
Being a burden or source of concern for others			
Yes	16.1	0.87 (0.38-1.98)	1.17 (0.63-2.16)
No	83.9	Reference	Reference
Losing respect of family or community			
Yes	11.3	0.95 (0.34-2.63)	0.62 (0.29-1.30)
No	88.7	Reference	Reference
Isolation or lack of support from family or friends			
Yes	9.5	0.33 (0.12-0.85)	0.37 (0.16-0.85)
No	90.5	Reference	Reference
Teasing or insulting			
Yes	8.0	2.09 (0.62-7.06)	0.93 (0.42-2.09)
No	92.0	Reference	Reference
Separation[d] from partner			
Yes	5.4	0.17 (0.05-0.57)	0.44 (0.15-1.31)
No	94.6	Reference	reference
Conflict with partner			
Yes	5.0	0.18 (0.05-0.67)	1.73 (0.58-5.15)
No	95.0	Reference	Reference
Losing customers or a job			
Yes	4.7	0.42 (0.11-1.66)	1.00 (0.36-2.76)
No	95.3	Reference	Reference

ART, Antiretroviral therapy; PMTCT, Prevention of mother-to-child transmission of HIV;
OR, Odds ratio; CI, Confidence interval.

[a] Partner i.e., spouse or steady sexual partner.
[b] Relative i.e., mother, father, sister, brother, child or other relative.
[c] Question asked more broadly to include general HIV care.
[d] Separation i.e., separation, abandonment, or divorce.
The multivariable logistic regression model was adjusted for age, educational level, marital- and cohabitation status, employment status, economic responsibility to other people, living with relatives, and time since HIV diagnosis.

4.2 PAPER II: THE EFFECT OF WEEKLY INTERACTIVE TEXT MESSAGING ON EARLY INFANT HIV TESTING

Between 25 June 2015 and 5 July 2016, 735 consecutive pregnant women were screened for study eligibility when they presented to PMTCT care at the six study sites. Of those screened, 88 were ineligible, mainly due to not having mobile phone access (n=51). In addition, 37 women were unwilling to participate, and 10 did not have time to be screened or enrolled. Of 600 women enrolled, 299 were randomly assigned to the intervention group and 301 to the control group (standard care). Participants' characteristics are presented in Table 3. More than half (54.0%) had secondary schooling or more. Most of the participants were married or living with a partner (81.3%) and diagnosed with HIV more than six months before trial enrolment (70.5%). Overall, baseline characteristics of pregnant women were balanced between the intervention and control group.

4.2.1 Early infant HIV testing

By eight weeks of age, 213 infants in the intervention group (85.5% of the 249 recorded live births) and 216 in the control group (84.7% of the 255 recorded live births) were tested for HIV. The proportion of infants tested by eight weeks of age out of all pregnant women enrolled (intention-to-treat analysis) was 71.2% in the intervention group and 71.8% in the control group. The WelTel intervention had no significant effect on the uptake of EID HIV testing by eight weeks of age compared to standard care (RR: 0.99; 95% CI: 0.90-1.10). Adjusting for age, time from HIV diagnosis, and site did not notably change the results (Table 4). When excluding participants with a miscarriage, stillbirth, infant or maternal death, or transfer to another clinic before eight weeks postpartum, similar results were observed (Table 4). By eight weeks of age, two infants in the intervention group (0.8% of recorded live births) and three in the control group (1.2% of recorded live births) were observed to be infected with HIV.

In an analysis of infants HIV tested between four to eight weeks of age (to reduce the effect of at birth HIV testing), 207 infants in the intervention group and 209 infants in the control group were tested (intention-to-treat RR: 1.00; 95% CI: 0.90-1.11). Adjusting for age, time from HIV diagnosis, and site did not notably change the results (Table 4). A sensitivity analysis excluding participants with a miscarriage, stillbirth, infant or maternal death, or transfer to another clinic before eight weeks postpartum gave similar results (Table 4).

In an exploratory subgroup analysis, there was no evidence of effect modification by age, educational level, marital and cohabitation status, time since HIV diagnosis, employment status, time to reach the clinic, HIV status disclosure to a partner, or HIV status disclosure to someone. However, at the UGDH study site, there was a significant interaction compared to the MTRH (reference) site, with improved EID HIV testing in the intervention group by eight weeks of age (RR: 1.59; 95% CI: 1.06-2.38; p=0.03) and between four to eight weeks of age (RR: 1.65; 95% CI: 1.08-2.50; p=0.02).

Table 3. Characteristics of pregnant women at study enrolment (n=600).

Characteristic	**Intervention group (n=299) n (%)**	**Control group (n=301) n (%)**
Age (years)		
18-24	67 (22.4)	69 (22.9)
25-29	79 (26.4)	89 (29.6)
30-34	83 (27.8)	83 (27.6)
35-44	70 (23.4)	60 (19.9)
	Mean = 29.6 SD = 5.9	Mean = 29.1 SD = 5.5
Education		
Primary schooling or less	147 (49.2)	129 (42.9)
Secondary schooling	105 (35.1)	120 (39.9)
Higher education	47 (15.7)	52 (17.3)
Married or living with a partner		
Yes	244 (81.6)	244 (81.1)
No	55 (18.4)	57 (18.9)
Time since HIV diagnosis		
< 6 months	93 (31.1)	84 (27.9)
≥ 6 months	206 (68.9)	217 (72.1)
HIV status disclosure to someone		
Yes	226 (75.6)	232 (77.1)
No	73 (24.4)	69 (22.9)
HIV status disclosure to partner[a]		
Yes	172/244 (70.5)	175/244 (71.7)
No	72/244 (29.5)	69/244 (28.3)
Travel time to clinic		
< 1 hour	214 (71.6)	208 (69.1)
≥ 1 hour	85 (28.4)	93 (30.9)
Mobile phone used in study		
Own phone	271 (90.6)	283 (94.0)
Another phone	28 (9.4)	18 (6.0)
Clinic of enrolment		
Chulaimbo	40 (13.4)	40 (13.3)
Huruma	23 (7.7)	25 (8.3)
Kitale	102 (34.1)	103 (34.2)
Matayos	3 (1.0)	2 (0.7)
MTRH	93 (31.1)	93 (30.9)
UGDH	38 (12.7)	38 (12.6)

SD, Standard deviation; MTRH, Moi Teaching and Referral Hospital; UGDH, Uasin Gishu District Hospital.

[a] Among participants who were married or living with a partner (n=488).

Table 4. The effect of the WelTel intervention on early infant HIV testing (n=600).

Outcome	Infant HIV testing 0-8 weeks of age	Infant HIV testing 4-8 weeks of age
Intervention group (n=299)	213 (71.2%)	207 (69.2%)
Control group (n=301)	216 (71.8%)	209 (69.4%)
Unadjusted RR (95% CI); p value	0.99[a] (0.90-1.10); p=0.89 1.00[b] (0.92-1.09); p=1.00	1.00[a] (0.90-1.11); p=0.96 1.00[b] (0.92-1.10); p=0.92
Adjusted RR (95% CI); p value	1.00[c] (0.90-1.10); p=0.95 1.00[d] (0.93-1.09); p=0.94	1.00[c] (0.90-1.11); p=0.94 1.01[d] (0.92-1.10); p=0.83

RR, Rate ratio; CI, Confidence interval.

[a] Unadjusted intention to treat analysis (n=600).

[b] Cases of miscarriage, stillbirth, death of infant, death or mother, or transfer before eight weeks postpartum excluded (n=531).

[c] Adjusted for age, woman's time since HIV diagnosis at enrolment, and site (n=600).

4.3 PAPER III: THE EFFECT OF WEEKLY INTERACTIVE TEXT MESSAGING ON RETENTION IN CARE

Paper III is based on the same study population previously described in paper II (Table 3). Women who had a recorded date of delivery received the WelTel intervention until a median of 24 (interquartile range [IQR] 23-24) months postpartum. The proportion of participants retained in care at 18 months postpartum was 210 of 299 (70.2%) in the intervention group and 207 of 301 (68.8%) in the control group (RR: 1.02; 95% CI: 0.92-1.14). Adjusting for age, time since diagnosis, and site gave similar results (Table 5). Excluding participants with a miscarriage, stillbirth, infant or maternal death, or transfer to another clinic before 18 months postpartum did not notably change the results (Table 5). In subgroup analysis, there was no evidence of effect modification by age, educational level, time since HIV diagnosis, marital and cohabitation status, HIV status disclosure, time to reach the clinic, or site.

Table 5. The effect of the WelTel intervention on retention in care at 18 months postpartum (n=600).

	Intervention n (%)	Control n (%)	RR (95% CI); p value	Adjusted* RR (95% CI); p value
Retention in care at 18 months postpartum	210/299 (70.2)	207/301 (68.8)	1.02 (0.92-1.14); p=0.697	1.03 (0.93-1.14); p=0.582
Retention in care at 18 months postpartum[†]	208/254 (81.9)	201/248 (81.0)	1.01 (0.93-1.10); p=0.809	1.02 (0.94-1.10); p=0.649

RR, Rate ratio; CI, Confidence interval.

*adjusted for the baseline characteristics age, time from diagnosis to enrolment, and site.

[†]excluded participants with a miscarriage; stillbirth; infant death; transfer to another clinic, or maternal death before 18 months postpartum (sensitivity analysis)

The effect of the WelTel intervention on secondary trial outcomes is presented in Table 6. There was a similar proportion of participants retained in PMTCT care in the intervention group (239/299; 79.9%) and the control group (235/301; 78.1%) between six and 12 months postpartum (RR: 1.02; 95% CI: 0.94-1.11). Moreover, there was a similar proportion of women in the intervention group (210/299; 70.2%) and the control group (209/301; 69.4%) who were linked to chronic HIV care (RR: 1.01; 95% CI: 0.91-1.12). In addition, a similar proportion of women in the intervention group (150/299; 50.2%) and the control group (155/301; 51.5%) delivered at a healthcare facility (RR: 0.97; 95% CI: 0.83-1.14). The proportion who dropped out of care by 30 months from enrolment was 89 of 299 (29.8%) in the intervention group and 92 of 301 (30.6%) in the control group (hazard ratio: 0.98, 95% CI: 0.73-1.31).

At the end of follow-up, four infants (1.6%) of 249 recorded live births in the intervention group and three infants (1.2%) of 255 recorded live births in the control group were infected with HIV. No adverse events were reported during the trial.

Table 6. The effect of the WelTel intervention on secondary trial outcomes (n=600).

	Intervention n (%)	**Control n (%)**	**RR (95% CI); p value**	**Adjusted[*] RR (95% CI); p value**
Retention in care between six and 12 months postpartum	239/299 (79.93)	235/301 (78.07)	1.02 (0.94-1.11); p=0.576	1.03 (0.95-1.11); p=0.499
Retention in care between six and 12 months postpartum[†]	231/258 (89.53)	225/254 (88.58)	1.01 (0.95-1.07); p=0.730	1.01 (0.95-1.07); p=0.679
Linkage to chronic HIV care	210/299 (70.23)	209/301 (69.44)	1.01 (0.91-1.12); p=0.831	1.02 (0.92-1.12); p=0.737
Facility delivery[‡]	150/299 (50.17)	155/301 (51.50)	0.97 (0.83-1.14); p=0.745	0.98 (0.84-1.13); p=0.754

RR, Rate ratio; CI, Confidence interval.

[*]adjusted for the baseline characteristics age, time from diagnosis to enrolment, and site

[†]excluded participants with a miscarriage; stillbirth; infant death; transfer to another clinic, or maternal death before 14 months postpartum (sensitivity analysis)

[‡]missing values for 88 participants in the intervention group and for 97 in the control group. Outcome not applicable for 48 participants in the intervention group and for 42 in the control group due to miscarriage, lost to follow-up, or transfer before infant was due. Analysis was intention-to-treat.

4.4 PAPER IV: THE USE, ADHERENCE, AND EVALUATION OF INTERACTIVE TEXT MESSAGING

The 299 women who had been randomly assigned to the WelTel intervention group (in papers II and III) constituted the study population of this cohort study, and their characteristics are described in Table 3. Of the 299 participants in the WelTel intervention group, 60 received the intervention shorter than intended due to miscarriage, stillbirth, death of the infant or the woman, withdrawal, technical reasons, or other reasons.

There were 31,640 text messages asking "Mambo?" (Swahili for "How are you?") sent to the participants. However, two of the 31,640 text messages were sent after a participant had withdrawn, and these two text messages with corresponding responses were therefore not included in the analyses. Thus, in the analyses of paper IV, there were 31,638 text messages that were sent to the participants for a median of 27 (IQR 25-29) months.

The women sent 15,183 (48.0%) okay responses, and 438 (1.4%) problem responses. There were 16,017 (50.6%) non-responses registered. The women sent a median of 54 (IQR 10-83) okay responses, 0 (IQR 0-2) problem responses, and had a median of 45 (IQR 20-83) registered instances of non-response. From the first month to the 28th month in the intervention (i.e., the median time of follow-up), the proportion of text messages indicating a problem decreased from 5.6% to 0.4%, okay responses decreased from 58.9% to 38.2%, and non-responses increased from 35.5% to 61.5%. A total of 147 of 299 (49.2%) women sent one or more text messages indicating a problem. The problems were mainly health related (83.9%), followed by social or domestic (5.4%), economic or financial (4.3%), psychological (3.6%), and need of information (2.2%) (Figure 8).

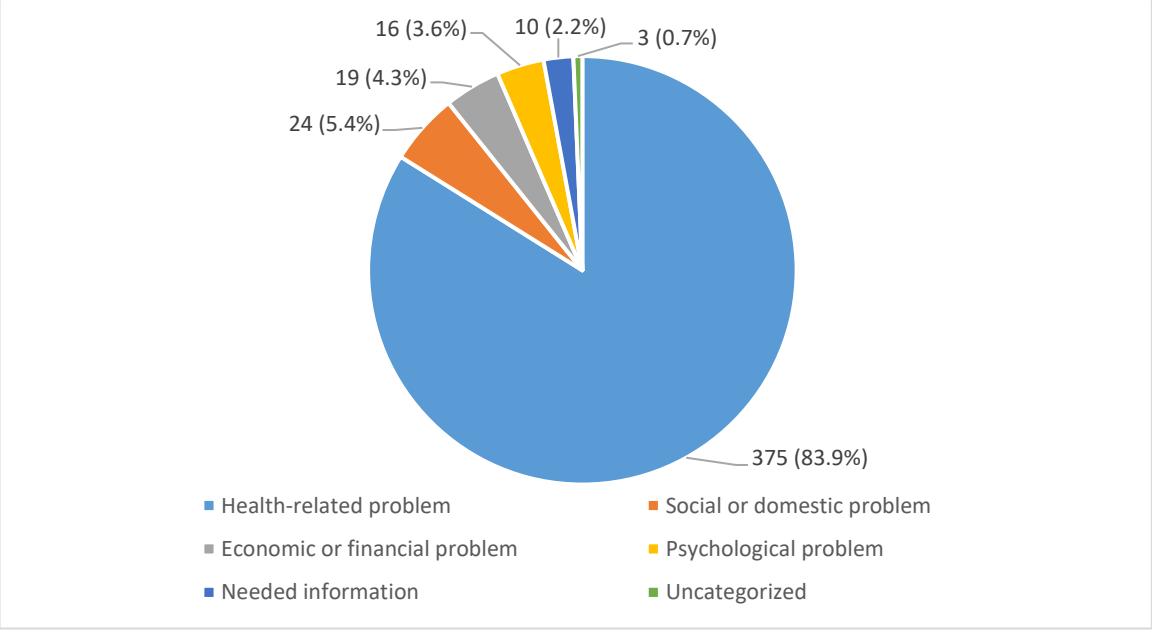

Figure 8. Women's reported problems in categories (n=447 problems reported by women in follow-up calls of 438 text message responses indicating a problem).

More than half of the text message problem responses (53.2%) were sent during the first six months of follow-up. The proportions of the text message responses indicating a problem out of text messages received were 3.3% during pregnancy and 1.1% during the postpartum period. However, the proportion of text messages indicating a problem increased from 2.6% the last month before delivery to 4.4% during the first month postpartum. It thereafter dropped again to 2.2% during the second month postpartum.

Participants who did not respond to the text messages explained in follow-up calls with healthcare workers that this was due to being busy or forgetting to respond (12.1%) or having a phone-related problem (9.1%). However, more than half of the participants who did not respond to the text messages did not answer the follow-up phone call (53.5%). There were 130 of 299 (43.5%) participants who responded to <50% of the text messages. Women with secondary schooling were more likely to send a text message indicating a problem (OR: 1.88; 95% CI: 1.08-3.27) compared to those who had primary schooling or less. Women aged 18-24 years were more likely to respond to <50% of the text messages (OR: 2.20; 95% CI: 1.03-4.72) compared to women aged 35-44 years. Women with higher than secondary education were less likely to respond to <50% of the text messages (OR: 0.28; 95% CI: 0.13-0.64) compared to women with primary education or less. Women who had disclosed their HIV status at study enrolment were less likely to have non-responses to text messages (RR: 0.77; 95% CI: 0.60-0.97) compared to women who had not disclosed their HIV status.

Of the 176 women who responded to the interviewer-administered questionnaire at 24 months postpartum, 93 (52.8%) strongly agreed and 74 (42.0%) agreed that the intervention had been helpful, and 129 (73.3%) reported that they wanted the text message programme to continue. Women reported that the greatest benefits of the weekly text messaging were improved communication and easy access to the healthcare workers (43.2%), that the healthcare workers cared for them (18.8%), and that the text messaging served as a reminder to attend clinic appointments (12.5%). Many participants reported that there were no barriers to receiving or responding to text messages (39.8%), whereas others reported that lack of phone access (15.3%), lack of battery power (11.9%), other phone-related problems (10.2%), or being busy or forgetting to respond (11.4%) were barriers to the interactive text messaging.

5 DISCUSSION

5.1 GENERAL DISCUSSION

The content of this thesis is based on the WelTel PMTCT trial in Kenya, which to our knowledge was the first RCT of participants in PMTCT care to investigate the effect of a text-messaging intervention with follow-up until 30-months postpartum. There was no intervention effect on early infant HIV testing (paper II), 18-months postpartum retention in care (paper III), or postpartum linkage to chronic HIV care (paper III). In exploratory subgroup analyses, there was overall no evidence of effect modification by baseline characteristics. There was, however, a significant effect of the intervention on early infant HIV testing at one of the small study sites, but there was no effect modification by study site in the subgroup analysis for 18-months retention in care. In line with our results, other RCTs published 2016-2022 reported no significant effects of text-messaging interventions on early (up to eight weeks) postpartum (98, 99), 12-month postpartum (115), or 24-months postpartum retention in PMTCT care (116). In contrast, earlier RCTs from Mozambique and Kenya reported that text messaging improved early infant HIV testing (95, 96) and maternal clinic attendance at eight weeks postpartum (95). We observed a higher uptake of early infant HIV testing (70) and a lower proportion of infants who were infected with HIV by eight weeks of age (117) both in the intervention and control group, compared to the national Kenyan estimates. Retention in care at 18 months postpartum was also higher than expected and in line with pooled estimates from a 2018 systematic review (21) and a 2021 RCT from Kenya (116), which suggests that retention in PMTCT care has improved in recent years compared to Kenyan studies and national data published 2011-2014 (118-120). The higher-than-expected retention in care in our trial may have attenuated any effect of the intervention on the trial outcomes, since the effect of an intervention not only depends on the implementation and the mechanism of impact, but also on the context in which the intervention is implemented (121). Improved retention in care may be due to several factors including decreasing barriers to the uptake and participation in PMTCT care, changes in society in HIV high-prevalence settings, general improvements in PMTCT care, and implementation of support mechanisms to improve retention in standard care. According to 2020 data, women in Kenya are close to achieving the UNAIDS' 95-95-95 target, with over 98% of women living with HIV being diagnosed, 92% accessing ART, and 94% of those on ART being virally suppressed (4). If these numbers are accurate and apply to all women throughout the PMTCT cascade, it represents a very rapid improvement in Kenya, indicating that within a few years the country will potentially be able to achieve the WHO's EMTCT target of ≤50 new infant HIV infections per 100,000 live births, and an HIV MTCT rate below 5% (122). However, given the disruptions of healthcare services caused by lockdowns related to the COVID-19 pandemic (123), setbacks in terms of HIV and PMTCT treatment outcomes in Kenya and other low- and middle-income-countries can be expected, though that is not yet evident in the available data. These disruptions may also have led to a relapse in

MTCT of HIV in SSA countries (124), and global initiatives to ensure access to COVID-19 vaccines must therefore be made a high priority to reduce the negative indirect effects of the pandemic on health systems and health outcomes in low- and middle-income countries (125).

5.2 DECREASING BARRIERS TO PARTICIPATION IN PMTCT CARE AND CHANGES IN SOCIETY

We observed (paper I) that a high proportion of participants had disclosed their HIV status to a partner, which is consistent with studies from Kenya published 2018-2019 (113, 126, 127). Compared to studies from Kenya published 2008-2014 (34, 49, 109, 128-131), HIV status disclosure to a partner appears to have increased. We also observed that women 18-24 years old were more likely to have disclosed their HIV status to a partner compared to women 25-44 years old. This could indicate an increased openness and less stigma related to HIV in younger couples, and potentially more male partner involvement for women in PMTCT care. Male partner support is important for women in PMTCT care to improve ART adherence, retention in PMTCT care, and to reduce MTCT of HIV (132-134). Our results on HIV disclosure are in line with a study from Tanzania (106), but in contrast to a study from South Africa, where younger women in PMTCT care were less likely to disclose to a partner (107). A study of non-pregnant women with HIV in Tanzania observed no association between age and HIV status disclosure (112). The discrepancy between the study results may be due to different study settings, women's marital and cohabitation status, and the age intervals used in the analyses, which differed between the studies.

Overall, we observed that most social concerns related to participation in PMTCT care were reported by only a small proportion of participants. This is in line with UNAIDS' data indicating a decrease of discriminatory attitudes toward people living with HIV in Kenya from 2009 to 2014 (57). Similarly, women in PMTCT care felt that HIV-related stigma had decreased in their communities, according to a study from Uganda (54). Despite these encouraging findings, we observed that stigma and social concerns continue to influence openness about HIV among pregnant women living with HIV. Continued interventions to decrease HIV-related stigma are therefore important in order to reach the fourth 90-goal of mental wellbeing and good quality of life for people living with HIV (135). It is also important to ensure the privacy and confidentiality of women living with HIV when they are visiting healthcare facilities to strengthen their trust in the health system, since concerns about involuntary HIV disclosure can limit women's access to PMTCT care (35) and lead to loss to follow-up (36). We also observed that concerns about isolation or lack of support from family or friends appear to be a barrier to HIV disclosure, consistent with a mixed-methods study from Tanzania where stigma in family and community was the most common reason for not disclosing HIV status among women in PMTCT care (56). Our results also suggests that concerns about conflict or separation from a partner are important to address when developing strategies to promote HIV disclosure (41, 53-56, 136). Support group counselling (137) or community interventions (138) to increase HIV disclosure to a partner should

consider focusing on women that are 25 years or older and women diagnosed with HIV during the past six months. Counselling and community interventions should support and empower women and reduce concerns about isolation or lack of support from family or friends as well as concerns about conflict and separation from a partner.

5.3 GENERAL IMPROVEMENTS IN PMTCT CARE AND SUPPORT MECHANISMS TO PROMOTE RETENTION IN CARE

The introduction and implementation of PMTCT Option B+ care has simplified treatment programmes, improved quality of care, led to earlier initiation of ART, improved maternal health outcomes, and reduced the risk of HIV transmission to infants and sexual partners (20). In addition, several nation-wide interventions to improve retention in PMTCT care have been implemented in Kenya in recent years (70, 103-105). The tracing of women who default scheduled appointments by phone calls or household visits (103, 104), peer-support and counselling by mentor mothers (70, 139), and integration of PMTCT care with general antenatal and postnatal care with the aim of reducing HIV-related stigma (70, 105) were three important interventions that were implemented in our study setting between 2005-2017. These interventions have improved the uptake and adherence to ART and have reduced loss to follow-up (140-142).

According to unpublished qualitative data from our trial, substantial informal phone communication between healthcare workers and patients took place during the course of the trial (143). This included text messaging to deliver laboratory test results and calls to remind patients of upcoming scheduled clinic appointments. Healthcare workers also provided patients with their personal contact information and allowed them to contact them about issues related to care at any time. These programmatic strategies were implemented for all women in PMTCT care in our study setting, regardless of participation in the WelTel PMTCT trial or study group allocation.

Text messaging and efficient patient tracking have previously been recommended by the WHO to improve retention in HIV care (144). The findings of this thesis do not contradict the WHO's recommendation, but in settings where the use of telecommunication and patient tracking already has been implemented and is extensively used in standard care, the added value of using resources to implement additional mHealth interventions aiming to improve long-term retention in PMTCT care may be limited.

5.4 USE OF AND ADHERENCE TO TEXT MESSAGING AND DESIGN OF INTERVENTIONS

Our results from paper IV suggest that the adherence to send text message responses was relatively low, gradually declining over time in the intervention. The long duration (over two years) of our intervention may be an explanation for the declining adherence to respond to interactive text messages relative to earlier interactive text-messaging interventions in HIV care in Kenya (86, 87) and Nigeria (145). Interactive, two-way text messages sent to people living with HIV less frequently than daily have been reported to better maintain participants' involvement and reduce text-messaging fatigue (146). However, our results suggest that the duration of our intervention was too long for participants to stay adherent to the intervention. Similar results have been reported in a previous trial of the WelTel intervention among adult women and men living with HIV (86, 88). We did not find any effect of the WelTel intervention on either early (paper II) or late (paper III) postpartum retention in PMTCT care. These similar results after shorter as well as longer exposure for the intervention could indicate that the decreased engagement to use and adhere to the intervention over time was not decisive for the null results in our trial.

There could be a decreased interest to stay engaged in an intervention when the same text message content is sent every week, which is supported by a study from the United States where there were fewer responses to static messages compared to dynamic messages such as quizzes and questions (147). A recent qualitative study has suggested that women in PMTCT care may prefer infrequent direct appointment reminders rather than repeated weekly messages (148). Educational or encouraging messages for emotional support may also be preferred (149). Consistent with these findings, interventions with a personalised message content have been reported to be more effective to improve ART adherence among people living with HIV (146). However, a 2022 cluster-RCT of 1,331 women in PMTCT care in Kenya reported that neither weekly, tailored, two-way text messages, nor two-way text messages combined with home visits by community-based mentor mothers, had any effect on 12-month postpartum retention in care or ART adherence (115). In line with this, a 2021 RCT of 824 women in PMTCT care in Kenya (116) reported that neither one-way nor two-way tailored text messages that were timed along the pregnancy and postpartum continuum (150, 151) had no effect on ART adherence, HIV viral suppression, on-time clinic attendance, or 24-month postpartum retention in PMTCT care. The two-way text messaging in that trial did, however, shorten time to postpartum contraception use, suggesting that the text messaging had a greater potential to influence early postpartum outcomes compared to long-term outcomes, where habituation may decrease the intervention effect (116).

Previous studies have often reported beneficial effects of mHealth interventions on short-term outcomes, whereas the long-term effects have been less studied (101, 152-155). A recent 2020 systematic review reported a significant effect of mHealth interventions on ART adherence or retention in HIV care in 56% of 27 studies from low- and middle-income countries (155). Interventions were more likely to have a beneficial effect on ART adherence rather than retention in care, but in many studies, ART adherence was self-reported and thus

less reliable (155). In addition, a 2019 systematic review emphasized that many text-messaging RCTs in HIV prevention and care have a significant risk of bias due to high attrition, lack of intention-to-treat analyses, and selective reporting (156).

We observed that less than half the participants in the intervention group reported a problem in a text message over a median of 27 months. There was an increased reporting of problems during the first month postpartum, but overall, the reporting of problems rapidly declined after a few months. The intervention appeared to be most useful for reporting problems related to the women's own or their infants' physical health. Our findings suggest that women with lower education may be less likely to report a problem in a text-messaging intervention. Educational level may be associated with awareness of health issues related to pregnancy and HIV, or mobile phone usage patterns. Limited reading and writing skills have also previously been reported to limit the use of text-messaging interventions in low- and middle-income countries (79). This was, however, less likely to be a barrier in our study, as the WelTel intervention was easy to use and required only modest reading and writing skills.

5.5 POTENTIAL BENEFITS AND IMPROVEMENTS DUE TO THE WELTEL INTERVENTION

In total, 59% of women who received the WelTel intervention responded to the interviewer-administered follow-up questionnaire at 24 months postpartum. Most of them thought that the intervention had been helpful, and they wanted it to continue. The greatest perceived benefit was that the intervention improved contact with, and facilitated access to, healthcare workers. Another benefit was that the intervention contributed to a feeling that the healthcare workers cared for them, which is consistent with previous findings from another trial of the same intervention among men and women enrolled in general HIV care (88).

5.6 POTENTIAL BARRIERS AND DISADVANTAGES ASSOCIATED WITH THE WELTEL INTERVENTION

Of those who were interviewed at the end of the intervention, 40% reported that there was no barrier to respond to interactive text messages. Among those who reported barriers, most were phone related. Around six percent of the participants in the intervention group withdrew from receiving text messages or from follow-up. All withdrawals occurred later than eight weeks postpartum, indicating a reduced perceived benefit of the intervention or a time-dependent fatigue to receive text messages. In unpublished qualitative interview data, some of the healthcare workers reported that the WelTel intervention relieved their work of contacting and communicating with participants, but opinions were divided (143). The many non-responses to text messages (paper IV) led to more work in terms of calling the non-responders. The benefit of these calls to non-responders is questionable, and the extra workload can decrease the perceived usefulness of an mHealth intervention among healthcare providers (157).

5.7 METHODOLOGICAL CONSIDERATIONS

5.7.1 Strengths

Our trial had several strengths. Our RCT had a relatively large sample size which increased statistical power and decreased the risk of both type I errors (to incorrectly reject a null hypothesis) and type II errors (to incorrectly fail to reject a null hypothesis) (158). Our RCT had a high participation rate and a multicentre design which included clinics spread over a large area in western Kenya with both urban and rural populations as well as a varying prevalence of HIV. This increased the generalisability (also known as external validity) of our findings (159). The baseline characteristics were balanced between the intervention and control group which indicates a successful randomisation. The RCT design provides advantages compared to other study designs in terms of minimising the risk of biases as well as known and unknown confounding factors, to properly assess the intervention effect between those exposed versus non-exposed for an intervention (159). The participants were not given any incentives to participate in the trial, and we relied on healthcare workers at the clinics to handle the mobile phone communication related to the intervention. This was done to resemble a real-life implementation. The long follow-up time from the first ANC visit to 30 months postpartum also makes our trial unique as it offered the opportunity to study retention in care along the entire PMTCT period as well as postpartum linkage to chronic HIV care. The use of many different data sources reduced the risk of drawing conclusions from invalid data, of importance to internal validity. We observed a good conformity and accuracy of the data collected from different sources. The validity of our results was also improved by the use of national NASCOP data, enabling us to capture viral load data for women and PCR tests for infants as evidence of retention in care outside the study clinics for the participants who had been transferred or self-transferred. All analyses of the papers were recalculated and double-checked by a statistician and/or co-authors to assure the accuracy of the results.

5.7.2 Limitations

The studies had several limitations. Due to the observational and cross-sectional design of paper I, we were not able to assess causality between participants' social concerns and HIV status disclosure. In addition, we were not able to exclude reverse causality. As we included women at their first visit in PMTCT care, the time in the intervention thus varied by gestational age at enrolment. Therefore, at early infant HIV testing (paper II), some women had been exposed to the intervention for many months whereas others, only for a few weeks. We did, however, assess the intervention effect on multiple endpoints from delivery to 30 months postpartum, with clear null results throughout the continuum of PMTCT care which indicates a limited impact of exposure time on our results. It is also worth to keep in mind that the low MTCT rate (i.e., the proportion of infants infected with HIV) in our trial is not fully comparable to the national MTCT rate in Kenya. In contrast to our trial population, the

national MTCT rate also includes MTCT from women who were unaware of their HIV due to not being HIV tested during pregnancy or acquiring HIV peripartum or postpartum.

5.7.3 Selection bias

Selection bias can influence the results of epidemiological studies and affect their internal or external validity (160, 161). The previously discussed good balance of baseline characteristics between the intervention and control group indicates that the randomisation was successful, and not subject to selection bias. This indicates that the internal validity of our trial was not affected by selection bias. Regarding the external validity, despite our high participation rate, it is possible that women who declined to participate had different characteristics related to social concerns, HIV status disclosure, and time since HIV diagnosis compared to those who were enrolled. This possible selection bias applies to all studies where not all screened participants are enrolled. A potential selection bias may thus have led to an underestimation of social concerns and an overestimation of HIV status disclosure in paper I. The results in our papers regarding HIV status disclosure (113, 126, 127), early infant HIV testing (98, 99), and retention in PMTCT care (116) were, however, in line with other contemporary studies, which indicates that any selection bias did not affect our results differently than other similar studies. In paper IV, we interviewed women when they attended a clinic visit at 24 months postpartum to evaluate the intervention. Due to miscarriages, stillbirths, infant or maternal deaths, transfers of care, or loss to follow-up among a substantial portion of women in PMTCT care, we can only generalise our interview findings to women who are retained in PMTCT care until 24 months postpartum.

5.7.4 Social desirability bias

Social desirability bias is a form of misclassification of an outcome, that possibly could have influenced our results deriving from participants' responses in the baseline and follow-up interviews (160). Social desirability bias can be caused by self-deception or impression management, the latter due to a desire to portray oneself with certain characteristics that are socially favourable or health-promoting (162). There is a risk of a social desirability bias in self-reported research, particularly when participants are interviewed face-to-face about sensitive topics such as social concerns, intimate partner violence, and HIV status disclosure. It is possible that women in our trial underreported some social concerns that they did not perceive to be socially acceptable. They may also have underreported non-disclosure of HIV status, since women in PMTCT care in Kenya are counselled and encouraged to disclose their HIV status to reduce the risk of sexual transmission of HIV (63). We did, however, observe a similar prevalence of HIV status disclosure compared to other recent studies (113, 126, 127), and it is thus likely that social desirability bias did not affect our results differently compared to other studies. It is also possible that a social desirability bias may have influenced the results of participants perceptions of the intervention (paper IV). The interviewers were,

however, instructed to be objective and to collect the data as accurately as possible, but there is still a risk that the participants found it more socially acceptable to give a positive evaluation of the intervention to the interviewers.

5.7.5 Information bias

Information bias can lead to systematic errors due to misclassification of data, and may arise during collection, handling, and recording of information in a study (163). Missingness of data can contribute to information bias. For many outcomes studied in this thesis (e.g., retention in care), only the event (e.g., being retained in care) was indicated in the data source, whereas the non-event (e.g., not being retained in care) was not indicated. Thus, to rule out whether lack of information in a single data source was due to a true non-event (e.g., not being retained in care) or due to missingness of data could be challenging. However, as previously discussed, we used multiple sources of data for most of the trial outcomes to decrease the influence of missingness on our results. For example, the 18-months retention in care outcome was based on different types of evidence of being engaged in care (164), which has been reported to improve the accuracy when estimating retention in care (165) and to reduce the impact of missing data. However, place of delivery was an outcome that only was indicated in one data source (the patients' files). There was no indication of whether the woman had delivered at a facility or at home for 88 women in the intervention group and 97 women in the control group, thus only a modest difference of missing values between the groups. We found a lower than expected rate of women who delivered at a facility compared to national Kenyan survey data (60), possibly due to missing data, but a national strike during a significant part of trial follow-up also limited access to facility delivery. In paper IV, more than 50% of the reasons for not responding to the text messages were missing, mainly due to not reaching those who didn't respond to sort out the reason. Thus, the proportion of reasons for not responding to the text messages should be interpreted with this in mind.

5.7.6 Confounding

A confounder is a factor that is associated with an exposure and an outcome of interest (160). We cannot exclude the possibility that an unmeasured or residual confounding factor could have been associated with HIV status disclosure and one or more of the covariates in our models in paper I. This could also have been the case in paper IV for the reporting of problems and non-responses, and their association with baseline characteristics. We adjusted, however, for multiple covariates known to be associated with the outcomes of papers I and IV to decrease the risk of confounding.

5.7.7 Behaviour modification due to participation in research studies

Participants' behaviour may be influenced by participation in a research study which potentially can influence behaviour-associated research outcomes (166). According to the Hawthorne effect, participants modify their behaviour when they know that they are under observation, in line with the expectations and what is considered socially desirable (166). This effect is difficult to control and estimate, and it is possible that it influenced the high retention in care results in both the intervention and control group. In addition to the Hawthorne effect, participant's behaviour can also be influenced by the sheer participation in an RCT, as e.g., interviews generate more attention compared to standard care outside a research study. Odeny et al. observed that participation in either the intervention or control group of a clinical mHealth trial was associated with significantly improved early infant HIV testing compared to not being enrolled in the trial (167). However, participants in the Odeny et al. trial were not randomly allocated to trial participation versus non-participation, and the results could thus have been influenced by a selection bias (167). Both the Hawthorne effect and the increased attention due to participation in an RCT could have influenced our results, possibly leading to more favourable outcomes in the control group compared to a background population of women enrolled in PMTCT care in Kenya.

5.7.8 Publication bias and the importance of publishing null results

It is a well-known phenomenon that authors are less likely to submit, and journals are less likely to publish studies with null results, which leads to a bias towards more published studies with significant results that may be perceived as more interesting (160). Publishing research with null results is, however, very important to ensure an effective use of research grants and healthcare resources (168), particularly in resource-limited settings. More intervention studies that report significant as well as null results of outcomes relevant to resource-limited settings are crucial to ensure effective use of healthcare and community resources in low- and middle-income countries. This is particularly true for properly designed RCTs in line with the CONSORT guidelines (169) reporting outcomes relevant for HIV care, PMTCT care, and MTCT of HIV in SSA.

6 CONCLUSIONS

- The WelTel intervention had no significant effect on the uptake of early infant HIV testing, 18-month retention in PMTCT care, or women's postpartum linkage to chronic HIV care. Nevertheless, the intervention was well-received among those who were interviewed at the end of the intervention; they reported that it improved access to and communication with healthcare providers. Evidence from this WelTel PMTCT trial and other RCTs from SSA published after the start of our trial in 2015 does not support the use of text-messaging interventions to improve retention in PMTCT care.

- Pregnant and postpartum women's use and adherence to a weekly interactive text-messaging intervention appear to decrease over time, probably due to habituation and intervention fatigue. Younger women and those with lower education appear be less likely to adhere to interactive text messaging.

- More pregnant women living with HIV in Kenya appear to have disclosed their HIV status to a partner, and younger women (<25 years old) appear to be more open about their HIV status to a partner compared to women 25 years or older. This could lead to more partner support for younger women in PMTCT care.

- Pregnant women's concerns about isolation or lack of support from family or friends, as well as concerns about conflict or separation from a partner, may be barriers to HIV status disclosure among pregnant women living with HIV in Kenya.

- Retention in PMTCT care at 18 months postpartum appears to have increased in recent years after implementation of the WHO's PMTCT Option B+ guidelines and other support mechanisms in standard care in Kenya.

7 POINTS OF PERSPECTIVE

To further improve outcomes of PMTCT care for women and their infants, the following recommendations should be considered based on the findings in this thesis:

- Community and healthcare interventions in Kenya are needed to further decrease HIV-related stigma, women' financial and social dependency on partners, and to empower pregnant women living with HIV so that they safely can disclose their HIV status to their partners and other key persons in their social networks. This support to women should address concerns about separation and conflict with a partner as well as concerns about isolation and lack of support from family and friends. It is also important to organise PMTCT services so that women's confidentiality is ensured, allowing for visits to PMTCT facilities without raising concern of involuntary HIV disclosure.

- In light of the evidence from this thesis, interactive text-messaging interventions may not further improve uptake of early infant HIV testing or retention in PMTCT care in settings where defaulter tracing and extensive use of mobile phone communication between healthcare workers and women already are part of standard care. Further studies may investigate the effect of interactive text-messaging interventions in settings where other support mechanisms are lacking. Interventions that run over a longer period of time may also be less effective due to habituation and intervention fatigue among participants. When interventions aiming to improve outcomes of PMTCT care are designed, the potentially lower use and adherence to mHealth interventions among younger women and women with lower education should be considered.

- The studies included in this thesis report a higher-than-expected retention in PMTCT care and a high uptake of early infant HIV testing compared to previous research and national Kenyan estimates. However, after the outbreak of the COVID-19 pandemic, it is essential that the negative effects of the lockdowns and the pandemic response on access to HIV testing and PMTCT services are mitigated. It is also crucial that general access to COVID vaccines is ensured in SSA countries, to allow for safe reopening of society and to liberate healthcare resources to focus on further improving outcomes of PMTCT care.

- Further research, including well-designed RCTs of interventions aiming to improve outcomes of HIV and PMTCT care in resource-limited settings, is needed. This includes replication trials and reporting of null results to overcome publication bias and to ensure effective use of healthcare resources in low- and middle-income countries.

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