WelTel PMTCT study

Statistical Analysis Plan

Updated March 21 2020

This is an update of the study protocol for the analyses of the endpoints of the WelTel study, a multicenter parallel-armed randomized controlled trial testing the effect of weekly text messages on retention in care among 600 women living with HIV enrolled into prevention from mother to child transmission of HIV (PMTCT) program during pregnancy and follow-up until 24 months postpartum (exit from PMTCT). However, data is collected from the medical records up to 30 months post-partum to allow for late data entry and linkage to care information. The women were recruited at their first antenatal care (ANC) visit in their current pregnancy at 6 public ANC clinics in urban and rural areas in western Kenya including Moi teaching and referral hospital (MTRH), Usain Gishu district hospital (UGDH), Huruma sub-district hospital, Kitale district hospital, Matayos health care centre, and Chulaimbo sub-district hospital.

Intervention

Participants were randomly allocated to the intervention or control group (standard care) at a 1:1 ratio. Participants in the intervention group received an automated weekly short text message in Kiswahili asking about their health-related wellbeing and were provided with an opportunity to request assistance starting from their first ANC visit until 24 months postpartum. The message "Mambo?" (Kiswahili for "How are you?") was sent on a fixed day of the week and allowed the participant to respond within 48 hours that they are "ok" ("sawa" in Kiswahili) or that they have a "problem" ("shida" in Kiswahili). All responses were recorded in a database. Messages of problems among participants were automatically forwarded to each clinic. In the clinics, a nurse or mentor mother experienced in PMTCT care called the participants for follow up and for triaging the problems. A list of participants who do not respond within 48 hours was prepared every week and sent to each clinic. A nurse or mentor mother then made follow up phone calls to find out why the participants did not respond and if they had any problems. The phone call outcomes were recorded in a log at each clinic.

Primary endpoint:

Retention in PMTCT care at 18 months: This is defined as mother/infant pairs for whom there is a record that the infant had their HIV status confirmed at 18 months of age by either antibody or PCR HIV test, or there is a record of a viral load (VL) PCR test of the mother, allowing a window period of 16-24 months after delivery for the infants as well as mothers tests (at or outside the selected clinics), or for whom there is a record of a clinic visit for the infant or mothers at 16-24 months post-delivery (at or outside the selected clinics). Information about HIV laboratory tests and clinical visits is collected from medical records and patient registries (the antenatal and HIV exposed infant registers) including the National AIDS and STI control program (NASCOP) database.

Secondary endpoints:

1.) Retention in care at 6 weeks postpartum defined as a recorded HIV PCR test of the HIV-exposed infants at 6 weeks postpartum with a window period of I. 0-8 weeks postpartum and II. 4-8 weeks postpartum (at or outside the selected clinics). The definitions of an early HIV test was modified after the study protocol was published. In the published study protocol an early HIV test was defined as HIV exposed infants tested for HIV within 8 weeks of birth, measured as HIV exposed infants with known HIV status at age 10 weeks. We changed this definition to infants tested 0-8 weeks postpartum to be in line with Kenyan national data reported to UNAIDS. This updated definition does more correctly reflects women-infant-pairs adherence to early infant HIV testing guidelines, and is not depending on turn-around times of laboratory analyses or inconclusive laboratory test results. The second definition, infants HIV tested between 4 to 8 weeks postpartum, was added to be in line with Kenyan HIV guidelines published 2018 where a test within 4 weeks after birth is defined as a birth test. Birth testing, often performed at birth or shortly after delivery, was piloted at some clinics during parts of the study period. Infants tested at birth are according to Kenyan HIV guidelines recommended to have a second test within 6 weeks of age or the first contact with healthcare thereafter. The definition of infants HIV tested between 4-8 weeks postpartum does therefore reflect women's and infants adherence to the 6 weeks testing recommendation, without the influence of delivery at a health care facility where birth testing was provided or not. Information about HIV testing is collected from medical records, patient registries and the NASCOP database.

2.) Retention in PMTCT care at 6-12 months postpartum is defined as a recorded HIV PCR test, HIV antibody test, VL test, or a clinic visit of the infants or mothers during a window period 4-14 months postpartum (at or outside the selected clinics). Information about HIV laboratory tests and clinical visits is collected from medical records and patient registries (the antenatal and HIV exposed infant registers) including the NASCOP database.

3.) Viral load measurements close to delivery is defined as having at least one VL measure 5 months prior or after delivery. Among women with VL measurements close to delivery viral suppression will be further evaluated. Information about VL measurements is obtained from medical records and the national Kenyan NASCOP database. Viral suppression is defined according to the current Kenyan guidelines: HIV RNA ≤400 copies/ml. Low viremia is defined as 401 - ≤1000 copies/ml. High viremia is defined as > 1000 copies/ml. If there is more than one measurement we use the closest to delivery.

4.) All viral measurements taken on women during the trial up to 30 months as collected from medical records and the national Kenyan NASCOP database. Any women with at least one VL measurement during this time will be included in the analysis.

5.) Women's linkage to chronic HIV care after the end of PMTCT defined as women who participated in PMTCT and have a recorded VL test or clinic visit for

chronic HIV care (or PMTCT care in case of a new pregnancy) at 24-30 months post-delivery. Information about HIV laboratory tests and clinical visits is collected from medical records and the national Kenyan NASCOP database and any available tracing data. A lack of any information to suggest a linkage will be assumed to not be linked.

6.) Within program facility-based deliveries will be defined according to the medical record data. A lack of a record of a within program facility-based delivery will be assumed to be a delivery outside of a within program facility.

Primary Analysis:

In our initial analysis, we will compare baseline characteristics of the study population by randomised intervention assignment to ensure that balance was achieved by the randomisation. We will report the mean (standard deviation [SD]) or median (first quartile, third quartile) for continuous variables, and count and percentages for categorical variables.

The primary analyses will compare the main effects of the mobile intervention on retention in care at 18 months using the intention-to-treat (ITT) sample include all subjects that were randomized in the study including all women who were randomised regardless of outcome as either retained in care or not.

An adjusted Poisson regression model with robust standard errors will be used to calculate the rate ratio (RR) and 95% confidence interval (CI) of retention in care for the randomisation to the mobile intervention or the standard of care adjusted for site. All data analysis are planned to be run using the STATA software. A p-value of two-sides 0.05 will be considered significant evidence of an effect of the intervention.

Sensitivity analyses for primary analyses.

We will additionally run an adjusted Poisson regression model with robust standard errors to calculate the RR and 95% CI of retention in care for the randomisation to the mobile intervention or the standard of care adjusted for age, time from diagnosis to enrollment, as well as site.

We will additionally run an adjusted Poisson regression model with robust standard errors to calculate the RR and 95% CI of retention in care for the randomisation to the mobile intervention or the standard of care adjusted site removing participants with a documented miscarriage, stillbirth, death of the child before the 18 months visit or transfer to another clinic before 18 months post-delivery.

We will also rerun the above imputing all stillbirths, miscarriages, deaths of the child before the 18 months visit and those transferred to another clinic before 18 months post-delivery with either the best case, all those randomized to intervention would have been retained and all those not receiving intervention would have been lost to follow-up, and the worst case, the opposite of this, to determine if these participants could have influenced the results. We will do analyses where the outcome is stillbirths, miscarriage, death and transfer out to another clinic as the outcome

between the two arms; we will run this analysis adjusted for site, age and time since diagnosis.

We will also investigate time in care up to 30 months using Cox regression for the time in care for each subject, to estimate the hazard ratio for drop-out from outcome care for the randomisation to the mobile intervention versus the standard of care, adjusting for site, age. Dropping out of care will be the event. This analysis will be ITT time will start at enrollment, women who have a stillbirth or miscarriage will be included in the analysis and will be censored at the time of pregnancy termination.

Secondary Analyses:

1.) To investigate the effect of the mobile intervention on 6 weeks early infant diagnostic HIV-testing, we will use an adjusted Poisson regression model with robust standard errors to calculate the RR and 95% CI of retention in care for the randomisation to the mobile intervention versus the standard of care adjusted for age, site, and time from diagnosis to enrollment. Participants with documented stillbirths or miscarriage as well as the death of the child or transfer to another clinic before the specified time-intervals will be excluded from the analyses.

2.) To investigate the effect of the mobile intervention on the retention in care at 6-12 months, we will use an adjusted Poisson regression model with robust standard errors to calculate the RR and 95% CI of retention in care for the randomisation to the mobile intervention versus the standard of care adjusted for age, site, and time from diagnosis to enrollment. Participants with documented stillbirths or miscarriage as well as the death of the child or transfer to another clinic before the specified time-intervals will be excluded from the analyses.

3.) To investigate the effect of the mobile intervention on having at least one viral load measurement at the time of delivery (±5 months), we will use an adjusted Poisson regression model with robust standard errors to calculate the RR and 95% CI of having viral load measurement for the randomisation to the mobile intervention versus the standard of care adjusted for age, site, and time from diagnosis to enrollment. Participants with documented stillbirths or miscarriage as well as the death of the child or transfer to another clinic before the specified time-intervals will be excluded from the analyses.

4.) To investigate the effect of the mobile intervention on mean viral load as well as the trajectory of viral load values during the period we will use linear mixed-effects models, with random intercepts for individuals, including time of measurement, randomisation and an interaction of the time and randomisation as well as adjusting for site, and age.

5.) To investigate the effect of the mobile intervention on the linkage to chronic HIV care after the end of PMTCT we will use adjusted Poisson regression model with robust standard errors to calculate the RR and 95% CI of viral suppression for the randomisation to the mobile intervention versus the standard of care adjusted for age, site, and time from diagnosis to enrollment.

6.) To investigate the effect of the mobile intervention on within program facility-based deliveries, we will use adjusted Poisson regression model with robust

standard errors to calculate the RR and 95% CI of viral suppression for the randomisation to the mobile intervention versus the standard of care adjusted for age, site, and time from diagnosis to enrollment.