Mobile WAChx: Evaluation of mHealth strategies to optimize adherence and efficacy of PMTCT/ART

NCT02400671

STATISTICAL ANALYSIS PLAN

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1. STUDY SUMMARY AND AIMS

Rationale:

In 2013, WHO recommended that all HIV-infected pregnant women receive lifelong antiretroviral therapy for prevention of mother-to-child transmission (PMTCT-ART). This approach provides treatment and prevention benefits but there are concerns about its risks if maternal retention in care or adherence falters. Mobile health (mHealth) SMS (short message system) messaging is an evidence-based intervention that has been shown to significantly decrease treatment failure in adult ART treatment programs in Africa and may provide an inexpensive, feasible approach to enhance PMTCT-ART outcomes while supplementing rather than adding to provider workload. Our overarching hypothesis is that investment in mHealth for retention and adherence in PMTCT-ART will provide cost-effective benefit in sustaining antiretroviral regimen efficacy and durability.

Design: A 3-arm, unblinded, randomized clinical trial (RCT) comparing the effects of unidirectional SMS (ie: "push" messaging to participant) vs. bidirectional SMS dialogue between participant and provider vs. control (no SMS) among HIV-infected Kenyan mothers in PMTCT-ART programs.

Population: Pregnant HIV-positive women ≥14 years old and ≤36 weeks pregnant.

Sites: Ahero Sub-district Hospital (Kisumu, Kenya), Bondo District Hospital (Kisumu, Kenya), Mathare North City Council Clinic (Nairobi, Kenya)

Sample Size: 825 women will be randomized (275 per study arm)

Duration: Follow-up through 2 years postpartum

Specific Aims:

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

a) Maternal retention in care, ART refills, virologic non-suppression, and ART drug resistance

b) Infant HIV infection and HIV-free survival

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

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

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

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

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

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

Note: this Statistical Analysis Plan focuses on AIM 1.

Clinical Trials registration: https://clinicaltrials.gov/ct2/show/NCT02400671

2. STUDY ENDPOINTS

Primary study endpoints:

1. **Virologic non-suppression** will be defined for the primary endpoint using plasma viral load cut-off HIV RNA ≥1000 copies/mL for primary endpoint based on sample detection limits. A secondary cutoff at assay limit of detection (20c/ml for plasma and 839c/ml for DBS) will also be assessed.
2. **Retention in care** will be assessed based on medical record review of clinic attendance for scheduled clinical visits. Retention will be defined per participant as the proportion of scheduled visits to date attended within 2 weeks of their scheduled time and will be evaluated at 12 and 24 months postpartum. Loss to follow-up will be defined as no clinical visits for at least 6 months and will be evaluated at 12 and 24 months postpartum. Initial analyses will examine the 0-365 day interval and the 0-730 day interval.
3. **Infant HIV-free survival** will be assessed using infant HIV test and infant mortality data.

Secondary endpoints:

1. **ART adherence** will be assessed based on pharmacy refill data. For each refill period throughout the study, the proportion of days covered will be based on timing of refill collection. Self-reported adherence will also be assessed at study visits using a standardized questionnaire of the number of pills missed in the last 30 days and calculating percent adherence based on the expected number of doses taken. Self-reported adherence will be compared in secondary analyses.
2. **Drug resistance** will be assessed as detection of drug resistance mutations from plasma of women with HIV RNA ≥1000 copies/mL using the Oligonucleotide Ligation Assay (OLA).

Table 2.1 Summary of primary and secondary endpoints

Primary Endpoints	**Indicator**	**Source**
Maternal virologic non-suppression	HIV RNA ≥1000 copies/mL	Maternal study visits at 6 wk, 6, 12, 18, 24 mo, and record abstraction for routine VL.
Retention Loss to follow-up	Seen within 2 weeks of scheduled visits Not seen in clinic for ≥6 months	Record abstraction for scheduled clinic visits throughout study.
Infant HIV-free survival	HIV DNA and antibody results, and mortality	Record abstraction, infant study visits, verbal autopsy.
Secondary Endpoints	**Indicator**	**Source**
Drug Adherence	Pharmacy: % days covered since last refill Self-report: % doses taken in last 30 days *pharmacy data viewed as primary analysis of secondary endpoint	Pharmacy: record abstraction throughout study Self-report: questionnaire at study visits
Maternal drug resistance	OLA	Resistance assay in mothers with virologic failure

3. SAMPLE SIZE CONSIDERATIONS

a. Analyses based on comparison of proportions

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

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

Intervention	Prevalence of outcome	Control			
		70%	**75%**	**80%**	**85%**
	85%	120	250	906	-
	90%	62	100	199	686
	95%	35	49	75	140

b. Analyses based on survival analysis

Assuming alpha=5%, power=80%, 2-sided test, 1:1:1 allocation ratio, with a sample size of 275 per arm, and 10% attrition, we will have sufficient power to detect a Hazard Ratio (HR) of ≤0.65 in virologic failure, assuming an incidence rate of 25 per 100 person years (pys) in the control arm; a HR of ≤0.55 in drug resistance, assuming an incidence rate of 15 per 100 pys in the control arm; a HR of ≤0.65 in loss-to-follow-up, assuming an incidence rate of 25 per 100 pys in the control arm; and a HR of ≤0.50 in infant HIV or mortality (inverse of HIV-free survival), assuming an incidence rate of 10 per 100 pys in the control arm.

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

HR	Incidence in control			
	10%	**15%**	**20%**	**25%**
0.65	593	396	297	238
0.60	435	290	218	175
0.55	327	218	164	131
0.50	251	167	126	101

4. USE OF INTENTION-TO-TREAT AND PER-PROTOCOL ANALYSES

Analysis of primary outcomes will be by intention to treat (all participants).

5. STATISTICAL ANALYSES

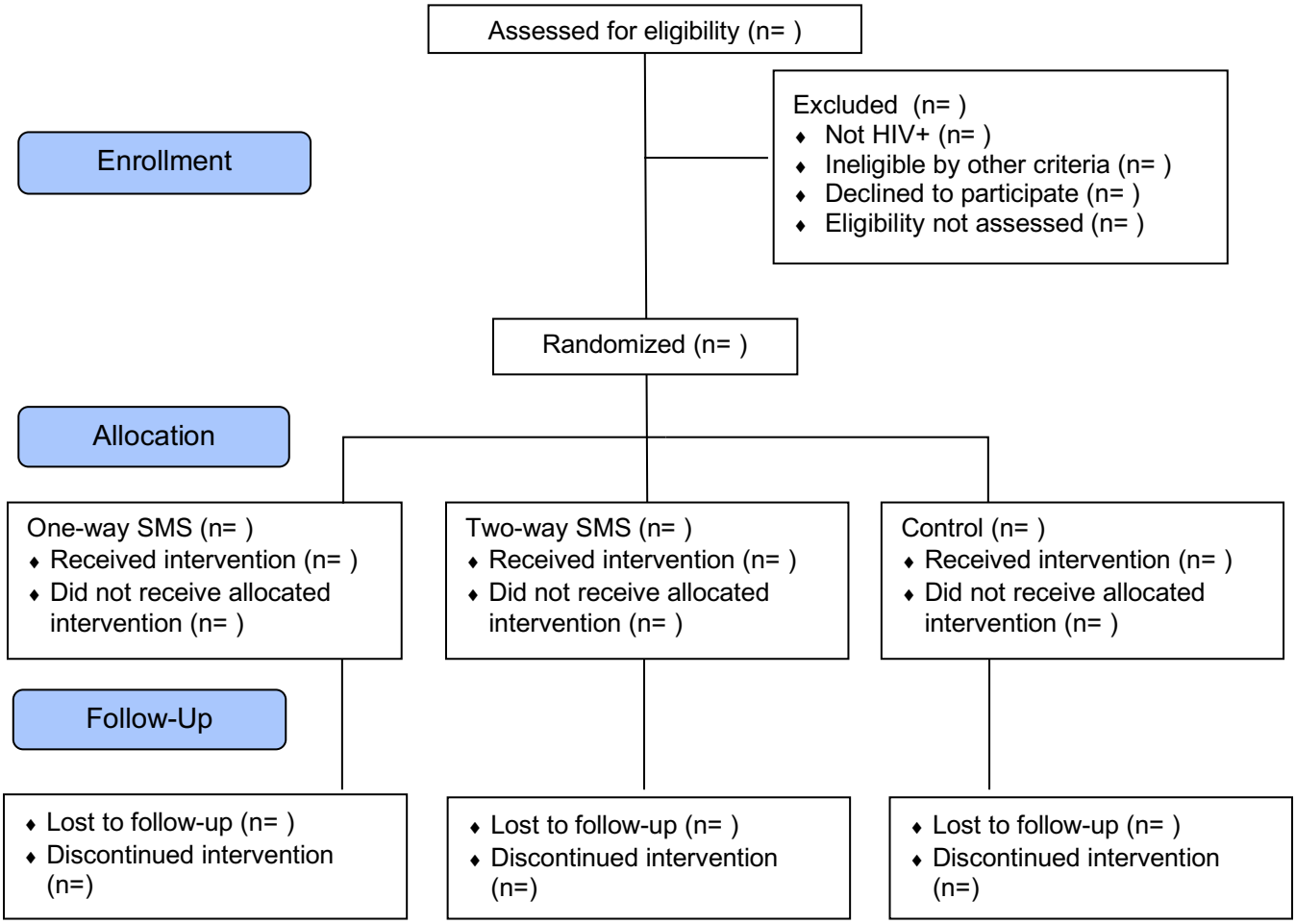
5.1 Study accrual

Per CONSORT guidelines, we will report the number of individuals who:

1. Underwent screening
2. Met inclusion criteria
3. Did not meet inclusion criteria (and reasons)
4. Enrolled in the study and were randomized
5. Treated as per study protocol

The number of individuals enrolled and randomized per study month will be presented in a figure by study arm. No formal statistical testing will be performed. See Figure 5.1.

Figure 5.1 – Trial profile



5.2 Baseline Characteristics

We will describe the distribution of baseline characteristics, using summary statistics appropriate for the measurement scale. We will present these summary statistics in tables both pooled and by study arm (see Table 5.2). To determine if the randomization resulted in balanced groups, baseline characteristics will be compared between randomization groups using Chi-square tests for categorical variables and the Kruskal-Wallis test for continuous variables.

Table 5.1 Baseline characteristics: shell table

	Overall	Control	One-way	Two-way
		n (%) or median (IQR)		
Clinic:				
Ahero				
Bondo				
Mathare				
Riruta				
Siaya				
Rachuonyo				
Sociodemographic				
Age (years)				
<8 years of education				
Monthly household income (KES)				
Married / cohabiting				
Employed				
Shares phone				
Can read SMS unassisted				
Can write SMS unassisted				
Obstetric				
Primigravida				
Pregnancy intended				
Gestational age (weeks)				
HIV/ART				
Time since HIV diagnosis (years)				
On ART				
Time since ART start (years)				
HIV status disclosed to partner				
ART regimen				
AZT + 3TC + NVP				
AZT + 3TC + EFV				
TDF + 3TC + LPV/r				
TDF + 3TC + NVP				
TDF + 3TC + EFV				
TDF + FTC + EFV				
Other				
VL ≥1000 copies/mL at enrollment				
Total				

Established ART (>4mo)
New ART (≤4mo)
CD4 at enrollment

5.3 Analysis of study endpoints

Analyses will be adjusted for baseline imbalances in randomization arms.

Primary

1. **Viral non-suppression (virus detected at ≥1000 copies/mL):** Generalized estimating equations (GEE) with log-binomial link will be used to compare the 2-way or 1-way arms versus control arm for prevalence of viral non-suppression at any time during follow-up. All available data will be used after enrollment and ≥4 months since ART start, but any observed unsuppressed VL within 30 days after an unsuppressed VL will be excluded. As secondary analyses, Andersen-Gill analysis will be used to compare incidence of viral non-suppression in the 2-way or 1-way arms versus control arm at any time during follow-up. The proportions of women ever experiencing viral non-suppression as well as the cumulative incidence by delivery, 180 days postpartum, 365 days postpartum, and 730 days postpartum will be compared between arms by log-binomial regression.
2. **Retention in care.** GEE with log-binomial link will be used to compare arms for proportion of visits attended within 2 weeks of scheduling throughout study follow-up. The proportions of women lost to follow-up by 12 and 24 months postpartum will be compared between study arms by log-binomial regression.
3. **Infant HIV-free survival**. Incidence of infant HIV acquisition or death will be compared between study arms using Cox proportional hazards regression.

Secondary

1. **ART adherence.** ART adherence will be compared in the 3 study arms using GEE. ART adherence postpartum will be compared as a continuous variable between study arms by ANOVA at 6, 12 and 24 months postpartum.
2. **Drug resistance.** Incidence of drug resistance on ART will be compared between study arms using Cox proportional hazards regression. Proportion of women with resistance will be compared at 24 months between arms using Chi square tests.

Table 5.2 Study endpoints: shell table

	Overall	Control	One-way	Two-way	p-value (one-way vs. control)	p-value (two-way vs. control)	p-value (either intervention vs. control)	p-value (one-way vs two-way)+
MATERNAL OPTION B+								
Virologic non-suppression ever (VL ≥1000 copies/mL) (n, %)								
$Prevalence of virologic non-suppression **								
&Incidence of virologic non-suppression (per 100 py)								
*With virologic non-suppression by delivery (%)								
*With virologic non-suppression by 180 days postpartum (%)								
*With virologic non-suppression by 365 days postpartum (%)								
*With virologic non-suppression by 850 days postpartum (%)								
Retention								
$Scheduled clinic visits attended on time since enrollment per participant (%)								
To 12 months postpartum								
To 24 months postpartum								
***Loss to follow-up (%)**								
By 12 months postpartum								
By 24 months postpartum								
^Infant HIV and mortality								
Infant HIV incidence (per 100 py)								
Infant mortality (per 1000 live births)								
Infant HIV-free survival (per 100 py)								

Drug resistance (DR)								
^Cumulative incidence of DR per 100 py								
*DR at 6 months postpartum (%)								
*DR at 12 months postpartum (%)								
*DR at 24 months postpartum (%)**								
Adherence								
$Self-reported adherence <95% over entire follow-up (%)								
$Refill-based adherence <95% over entire follow-up(%)								

$ Compared by GEE Log-binomial regression

& Compared by Andersen-Gill regression

^ Compared by Cox proportional hazards regression

* Compared by Log-binomial regression

+ Exploratory comparison

** All available VL after enrollment and ≥4 months after ART start will be included

5.4 INTERIM ANALYSIS

An interim analysis for maternal virologic suppression and failure and infant HIV-free survival will be performed using O'Brien-Fleming boundaries for benefit and futility when 50% of expected person time has been accrued.

5.5 MISSING OUTCOME DATA

While we will attempt to trace all study participants at 24 months postpartum, we anticipate that VL data may be incomplete due to participant loss to follow-up – either due to loss from care, or silent transfer to another facility. Due to the level of missingness we expect, we will not conduct any formal imputation. We will conduct sensitivity analyses for infant HIV-free survival assuming all infants who were lost to follow-up acquired HIV or died immediately after birth or survived HIV-free to 24-months postpartum.

5.6 SAFETY MONITORING

Adverse and severe adverse events, including social harms such as violence or breach of confidentiality, will be monitored, and unblinded results will be reviewed by the DSMB. The DSMB will make recommendations regarding any imbalances in safety outcomes.

Table 5.3 Adverse and severe adverse events: shell table

SAE #	PTIDNO	SAE description	Severity (Grade)	Onset date	Duration (days / unresolved)	Onset since randomization (days)	Relatedness to study

6. MODIFICATIONS TO ANALYSIS PLAN

Table 6.1 records modifications made to the analysis plan, and their justification.

Table 6.1. Summary of modifications

Description of modification	Date of modification	Modified SAP version	Original approach	Updated approach	Justification
Addition of secondary analysis with imputation of missing data (see section 5.5)	27 May 2018	3.0	None specified	A secondary analysis will be performed using multiple imputation by MCMC to impute VL 6 months after the time of last measurement.	Upon further thought, the study team realized that VL data were likely to be missing not at random and an imputed analysis could provide a less biased effect estimate.
Analytical approach for virologic failure primary outcome (see section 5.3)	1 May 2019	4.0	Incidence of virologic failure (HIV RNA ≥1000 copies/mL) after the first 4 months post-enrollment will be compared between study arms using Cox proportional hazards regression.	We will stratify the study population by VL at enrollment, and conduct 2 separate survival analyses: 1. Incidence of virologic suppression among participants with unsuppressed VL at enrollment. 2. Incidence of virologic failure among participants with suppressed VL at enrollment.	Our study population is composed of two distinct groups: those entering the study on established suppressive therapy, and those not on suppressive therapy. The study team realized that the intervention may have distinct mechanisms of action for each group. We will therefore analyze them separately.
Addition of pre-specified secondary analysis of virologic failure (see section 5.7)	1 May 2019	4.0	None specified	Among participants who are virally suppressed at 6 months postpartum, incidence of virologic failure (HIV RNA ≥1000 copies/mL) will be compared between study arms using Cox proportional hazards regression	This analysis will evaluate effects of SMS on longer term viral failure after the early postpartum period.

Addition of VL cutoff for virologic failure outcome (see section 5.3)	26 May 2020	5.0	Virologic failure = HIV RNA ≥1000 copies/mL	Virologic non-suppression = HIV RNA ≥1000 (primary) and ≥ assay limit of detection (secondary)	Since the study was originally funded, it is understood that levels below 1000 c/ml may be associated with transmission, so there is interest in additional analysis of lower cutoffs.
Modification of VL analysis approach	26 May 2020	5.0	We will stratify the study population by VL at enrollment, and conduct 2 separate survival analyses: 1. Incidence of virologic suppression among participants with unsuppressed VL at enrollment. 2. Incidence of virologic failure among participants with suppressed VL at enrollment.	Risk of virologic non-suppression will be analyzed as a repeated measure by GEE with Poisson link. Previously specified analyses of incidence of virologic suppression and virologic failure will be performed as exploratory analyses.	The stratified analysis did not use all available data, or allow us to probe changes in the intervention's effect over time. In order to maximize power and allow estimation of effect modification by peripartum timepoint, we will treat virologic non-suppression as a repeated measure.
Removal of secondary analysis with imputation of missing VL data	26 May 2020	5.0	A secondary analysis will be performed using multiple imputation by MCMC to impute VL 6 months after the time of last measurement.	No imputation will be performed.	Our dataset has 10% missing data at 24 months postpartum but >40% missing data at 18 months postpartum. Imputation of the one final VL measure would not address the problem of missing VL for a repeated measures analysis, since the bulk of missingness is at intervening timepoints. Imputation of intermediate VL given such high levels of missingness is not advisable.