Analysis Plan for

**Improving Adherence to ART at Reproductive and Child Health Clinics Integrating Option B+ in Tanzania**

Our main analytic method will be interrupted time series (ITS) with comparison series analysis,[[1]](#footnote-1),[[2]](#footnote-2) comparing changes in clinic attendance and medication adherence in the intervention and control groups from 12 months before to 7 months after initial intervention implementation. We will use both aggregate and individual level ITS models.7,[[3]](#footnote-3) To evaluate changes in time until gaps in clinic attendance and time until loss to follow-up, we will use Kaplan-Meier survival curves with accelerated failure time models,[[4]](#footnote-4),[[5]](#footnote-5) to compare pre- and post-intervention adjusted survival curves in the intervention and control groups.

Random allocation of health facilities to receive the intervention is our primary strategy to increase internal validity and strengthen causal inference about intervention effects; pre-post changes in randomly assigned control facilities will represent the counterfactual, while pre-post changes in intervention facilities minus pre-post changes in control facilities will represent intervention effects. Random allocation minimizes the likelihood of selection bias as well as most other threats to internal validity.[[6]](#footnote-6),[[7]](#footnote-7) By assigning facilities to district pairs, we maximize geographic separation between facilities to minimize contamination. In addition, while ITS with comparison series analyses of group-randomized clinical trials has been shown to produce results that are generally equivalent to more typical difference-in-difference analyses of randomized clinical trial designs,[[8]](#footnote-8),[[9]](#footnote-9) this type of longitudinal analysis has the additional advantage of being able to also adjust for differences in pre-intervention trends between groups, which are commonly observed in group-randomized trials with relatively small numbers of groups.[[10]](#footnote-10) ,[[11]](#footnote-11) Furthermore, ITS analysis can detect dynamic effects that increase or decrease over the course of the post-intervention period, which may occur during and after the period of post-intervention supervisory visits. Similarly, segmented survival models of time until gaps in clinical attendance and dropout can establish the equivalence of the baseline hazard functions in the intervention and control groups prior to the intervention and compare changes in hazard functions between groups post intervention (see Figures 1 and 2).



All women on ART in the RCH facilities in the intervention districts will receive the intervention. Our analytic sample will include all women (up to 200) who received ART at any time during the baseline period prior to the initial assessment (including women who had discontinued ART at the time of the assessment). We will capture data on all visits by these women to the sampled health facilities during the entire study observation period. Our individual-level ITS and survival models will use data on patient demographics and clinical characteristics to adjust for differences between intervention and control groups and to accommodate changes in the study population over time.

Our primary outcome will be missed clinic visits on the scheduled day, as measured from data in clinic records. Secondary outcomes will include: clinic attendance within three days and seven days of scheduled date; monthly percentage of days covered by dispensed ARVs; time until occurrence of a gap in clinic attendance of 15 or more days; time until loss to follow-up, defined as no clinic contact for the previous 60 days; and retention rates, defined as no clinic visit within 60 days of a missed appointment. All outcomes will be calculated from fields related to dates of visit attendance and medications dispensed in the standardized clinic record used in both intervention and control clinics.

To examine unadjusted changes in level and trend of use in our outcomes measured as rates (3 measuring missed visits at 1, 3 and 7 days; monthly percentage of days covered by dispensed medications), we will first create monthly time series comparing intervention and control groups. We will then test the statistical significance of level or trend changes following the intervention using individual-level General Estimating Equations models, adjusting for the correlation of different visits within patient, different patients within clinic, and first-order autocorrelation between sequential monthly measurements using the empirical sandwich estimator. Our analytic model for our primary outcome compares temporal changes in the odds of missing a visit before and after the intervention between intervention and control groups. An example of a model would be:

Missed visitt = 0 + β1\*group + β2\*montht + β3\*period + β4\*period\*montht + β5-n\*interaction(s) with group + ∑(confounders)

In this model, β1 represents baseline differences in odds of missing appointments between groups; β2 the baseline trend in odds; β3 the post-intervention level change in odds across all study groups; β4 post-intervention trend change in odds in all study groups. The parameters β5-n represents interaction terms of interest, including of group with period and period\*month; these represent the relative change in odds in the intervention group and thus measure the effects of the intervention. If the interaction of group with period\*month is not significant, we will drop the term, reducing the models to different-in-difference models. In all statistical models, we will include additional covariates to adjust for study group differences, which are common in group randomized trials. These will include: age, parity, duration of HIV infection, duration of previous treatment, WHO stage at start of treatment, CD4 count at start of treatment, and weight at start of treatment. We will retain predictors in the model only if they are meaningful predictors (P<0.10) of study outcomes.

Our Cox proportional hazards survival models examining changes in time until gap in attendance of 15 days or dropout will be conceptually similar, examining changes in the differences in hazard ratios between study groups from before to after the intervention. We will censor all women participating in the pre-intervention analyses at the data of dropout or at the date of the intervention; all women still in treatment at the time of the intervention will participate in the post-intervention analyses, censoring at date of dropout or at the end of the study period. We will evaluate the same array of covariates for inclusion in the models.

Qualitative data will be collected by trained interviewers not connected with the intervention. Interview material will be transcribed, coded, and checked for coding consistency using a framework of relevant themes that addressed key issues defined by our study objectives. Codes will be reviewed and grouped into categories and themes for analysis.The main themes will be perceived barriers and facilitators to clinic attendance and medication adherence; issues and challenges in implementing the appointment and community outreach systems; and successes and failures of the intervention. Additional themes will be allowed to emerge during analysis.

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4. Hosmer DW, Lemeshow S. Chapter 7. Extensions of the Proportional Hazards Model. Applied Survival Analysis. John Wiley & Sons, NY: 1999. [↑](#footnote-ref-4)
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6. Shadish, Cook TD, Cambell DT. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. Boston; Houghton Mifflin.: 2002. [↑](#footnote-ref-6)
7. Rossi PH, Lipsey MW, Freeman HE. Evaluation: A Systematic Approach (7th ed.). Los Angeles; SAGE Publications: 2004. [↑](#footnote-ref-7)
8. Fretheim A, Soumerai SB, Zhang F, Oxman AD, Ross-Degnan D. Interrupted time series analysis yielded an effect estimate concordant with the cluster-randomized controlled trial result. Journal of Clinical Epidemiology 2013 Aug;66(8):883-7. [↑](#footnote-ref-8)
9. Fretheim A, Zhang F, Ross-Degnan D, Oxman AD, Cheyne H, Foy R, Goodacre S, Herrin J, Kerse N, McKinlay RJ, Wright A, Soumerai SB. Cluster Randomized Trials versus Interrupted Time-Series: A comparative study of methods for evaluating health system interventions. (in revision) [↑](#footnote-ref-9)
10. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002 Aug; 27 (4):299-309. PMID: 12174032. [↑](#footnote-ref-10)
11. Cook TD, Campbell, DT. Quasi-Experimentation: Design and Analysis Issues for Field Settings. Boston: Houghton Mifflin; 1979. [↑](#footnote-ref-11)