STATISTICAL ANALYSIS PLAN

Simplifying Treatment and Monitoring for HIV *(STREAM HIV)*:
Point-of-Care Urine Tenofovir Adherence and Viral Load Testing to Improve HIV Outcomes in South Africa

"STREAM HIV Study"

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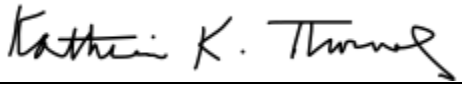	***20 November 2023***
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1 Abbreviations

ANC	antenatal care
ART	antiretroviral therapy
CCMDD	Central Chronic Medicines Dispensing and Distribution
CI	confidence interval
CRF	case report forms
DBS	dried blood spots
EAC	enhanced adherence counselling
HR	hazard ratio
IRR	incidence rate ratio
IQR	interquartile range
LTFU	lost to follow-up
PLHIV	people living with HIV
POC	point-of-care
PCZ CDC	Prince Cyril Zulu Communicable Disease Centre
RR	relative risk
SD	standard deviation
SoC	standard of care
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate
VL	viral load
VS	viral suppression

2 Introduction to the SAP

This statistical analysis plan (SAP) describes the plans for statistical analyses which will address the protocol objectives of the study, except for acceptability and cost effectiveness objectives, which are to be addressed using non-statistical analytic methods and are outside the scope of this document. Unblinding of outcomes summarized by randomized group will not be performed until after the SAP has been completed. Any subsequent changes to the SAP and timing relative to unblinding data summaries by randomized group will be noted in subsequent versions of the SAP.

3 Study Schema and Objectives

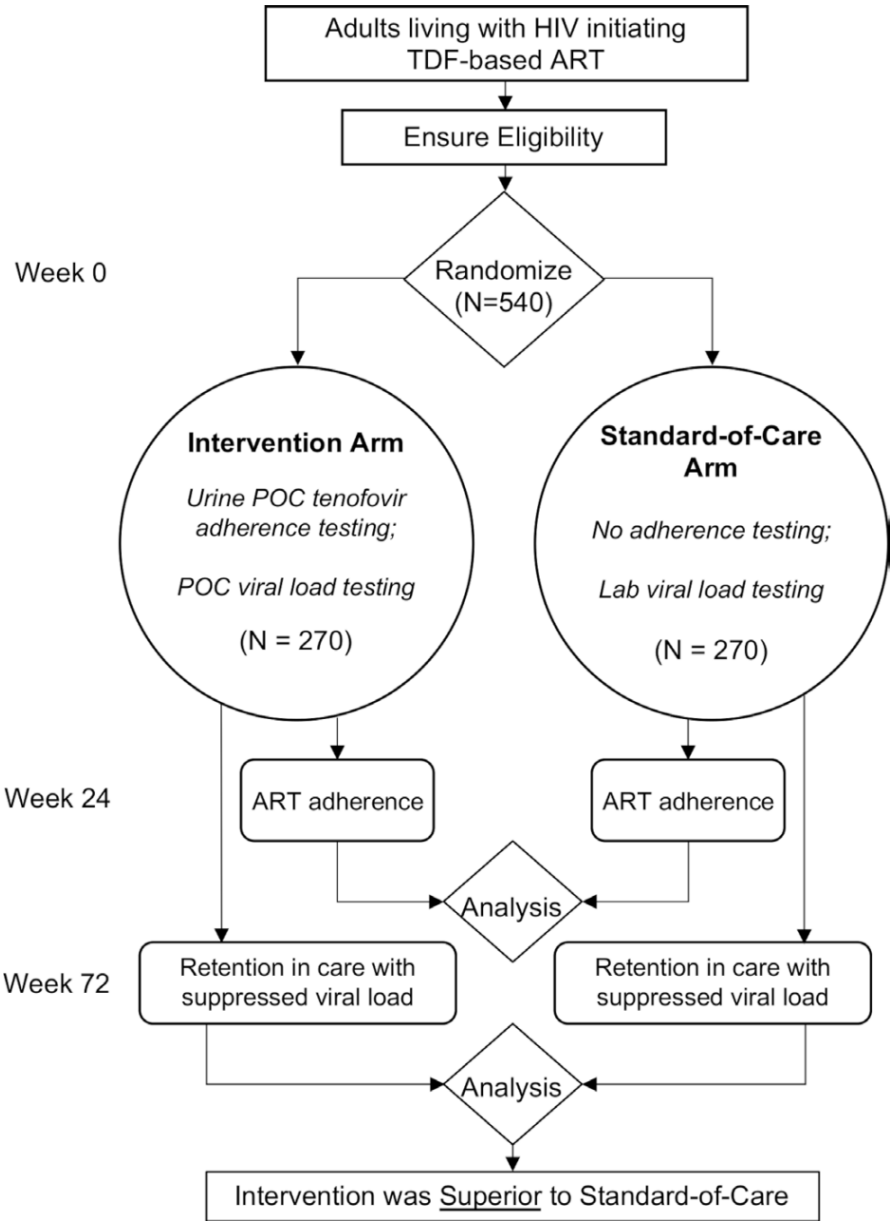
Purpose:	To determine the clinical efficacy, acceptability, and cost effectiveness of implementing an integrated model for HIV monitoring using point-of-care (POC) tenofovir (TFV) adherence testing with POC HIV viral load (VL) monitoring for improving adherence and outcomes among people living with HIV (PLHIV) who initiate first-line tenofovir disoproxil fumarate (TDF)-based ART in South Africa.
Design:	A Phase IIb open-label randomized controlled trial to assess routine POC TFV adherence testing with POC VL monitoring against the standard-of-care (SoC) with no objective TFV adherence testing and SoC VL monitoring. HIV-positive individuals (≥16 years) will be randomized 1:1 to the intervention versus SoC.
Central Hypotheses:	Our central hypotheses are that POC TFV adherence testing combined with POC VL monitoring will improve adherence to ART, VL suppression rates, and retention in care, while being feasible, acceptable, and cost-effective.
Primary Objectives:	• To determine if implementing routine POC TFV adherence testing is superior to SoC (no adherence testing) in improving ART adherence at 24 weeks after ART initiation among PLHIV receiving TDF-based ART in South Africa. • To determine if implementing routine POC TFV adherence testing in combination with routine POC VL monitoring is superior to SoC VL monitoring (with no adherence testing) in improving retention in care and VL suppression (<200 copies/mL) at 72 weeks after ART initiation among PLHIV initiated on first-line TDF-based ART in South Africa.
Secondary Objectives:	• To determine if implementing routine POC TFV adherence testing in combination with routine POC VL monitoring is superior to SoC VL monitoring (with no adherence testing) in improving retention in care and VL suppression (<200 copies/mL) at 24 weeks after ART initiation among PLHIV receiving TDF-based ART in South Africa. • To determine if implementing routine POC TFV adherence testing in combination with routine POC VL monitoring is superior to SoC VL testing (with no adherence testing) in improving ART adherence at 72 weeks after ART initiation among PLHIV initiated on first-line TDF-based ART in South Africa. • To assess the acceptability of POC VL and TFV adherence testing among PLHIV and providers. • To assess the cost-effectiveness of providing POC VL and TFV adherence testing to PLHIV as compared to SoC VL monitoring.
Population:	HIV-positive individuals (≥16 years) initiating a first-line, TDF-based ART regimen.
Study Sites:	1. HIV clinic at the Prince Cyril Zulu Communicable Disease Centre (PCZ

	CDC), which is located adjacent to the CAPRISA eThekwini Clinical Research Site and near the transport hub for public commuters in central Durban. The Lancers Road clinic, in close proximity to the PCZ CDC clinic, was added as a recruitment site for enrollments at the PCZ CDC clinic. 2. Primary Care Mafakathini Clinic adjacent to the CAPRISA Vulindlela Clinical Research Site, near Howick in rural KwaZulu-Natal. This clinic serves a rural community and provides primary health care including HIV care.
Study Size:	270 in each arm, for 540 total participants.
POC Testing:	GeneXpert® by Cepheid with the Xpert® HIV-1 VL cartridge. POC urine TFV adherence assay by Abbott.
Primary Outcome Measurements:	A. Tenofovir diphosphate concentrations in dried blood spots (continuous) at the 24-week visit after ART initiation and study enrollment B. Composite measure of requiring both HIV VL suppression and retention in care (binary) at study clinic at study exit (72 weeks after ART initiation) - Retention in care at study clinic (binary): collecting ART from the study clinic (or from community pick-up point under supervision of the study clinic) at study completion (72 weeks). - HIV VL suppression (binary): HIV VL <200 copies/mL by a lab-based reference assay at the study exit visit (72 weeks)
Study Duration:	4 years including enrollment period, and 72 weeks of follow-up per participant.

4 Study Design

The STREAM HIV study is a Phase IIb open-label randomized controlled trial with 540 participants randomized 1:1 to either the intervention or control group. Co-primary endpoint comparisons are planned at 24 weeks (adherence co-primary endpoint) and at 72 weeks (composite care measure co-primary endpoint).

The two co-primary endpoints are collected to answer separate research questions; the 24-week TFV-DP will address whether providing monthly POC TFV adherence testing for the first five months following ART initiation supports better adherence, while the 72-week retention-in-care and viral suppression endpoint addresses whether using monthly POC TFV adherence testing in the first five months followed by six-monthly POC VL testing, supports better long-term outcomes. With this in mind, we will not adjust either comparison for multiple testing but will interpret each result in the context of the other.


Adults living with HIV initiating TDF-based ART
Ensure Eligibility
Week 0
Randomize (N=540)
Intervention Arm
Urine POC tenofovir adherence testing;
POC viral load testing
(N = 270)
Standard-of-Care Arm
No adherence testing;
Lab viral load testing
(N = 270)
Week 24
ART adherence
ART adherence
Analysis
Week 72
Retention in care with suppressed viral load
Retention in care with suppressed viral load
Analysis
Intervention was Superior to Standard-of-Care

5 Sample size and power

72-week outcome. We calculated sample size and power estimates for comparison of the co-primary clinical outcome of viral suppression and retention in care at 72 weeks between the intervention and control arms using a Fisher's exact test, and this calculation was used to power the study. We estimate that 75% of control arm participants and 85% of intervention arm participants will achieve the combined outcome of viral suppression and retention in care based on our recent study that evaluated the effect of POC VL monitoring and healthcare worker task shifting on viral suppression and retention in care (Drain et al 2020). To have 80% power to detect a 10% difference (75% vs 85%) in achieving the primary outcome between the intervention and control arms using Fisher's exact test with a two-sided alpha of 0.05, we estimated that we would need to enroll 270 participants per study arm for a total of 540 participants (Table 1). We have not accounted for loss-to-follow-up in this calculation; because we will interpret those who are lost to follow-up as not retained, we expect all participants will have an outcome for analysis.

Table 1. Sample Size and Power Estimates using Fisher's Exact test

Outcome for SoC arm	Outcome for Intervention arm	Power (beta)	Sample size per arm	Total sample size
75%	82.5%	80%	493	986
75%	83.0%	80%	431	862
75%	83.8%	80%	353	706
75%	**85.0%**	**80%**	**270**	**540**
75%	87.0%	80%	183	366
75%	89.0%	80%	131	262

24-week outcome. We also calculated power estimates for comparison of the co-primary outcome of mean TFV-DP concentration at 24 weeks between the intervention and control arms using a t-test. Based on a study among PLHIV in South Africa recently initiating TFV-based ART regimen (Warne et al 2015), we assume that the mean TFV-DP concentration for control arm participants will be approximately 1000 fmol/punch with a standard deviation (SD) of 490. If we have 10% loss to follow-up (LTFU), we estimate that our sample size of 270 participants per study arm (243 after LTFU) will provide 80% power to detect a mean difference of 125 fmol/punch between the intervention and control arms.

6 Population and Data Source

Participants enrolled in the STREAM HIV Study: Five hundred forty (540) PLHIV who initiate first-line TDF-based ART in South Africa. Any randomized participants subsequently found to be ineligible will be reviewed by a statistician blinded to the participant's randomized group to determine inclusion in the study population for analysis. The data sources for the analyses are the study's Case Report Forms (CRFs) as entered into DFDiscover, as well as relevant study laboratory results which may be entered into DFDiscover or imported into DFDiscover, as appropriate.

7 Outcome Definitions

7.1 Co-Primary Outcomes

The two co-primary outcomes for the trial are

1) Primary Outcome at 24 weeks post-enrollment. Tenofovir-diphosphate (TFV-DP) concentrations (continuous) in whole blood dried blood spots (DBS) by a lab-based assay (liquid chromatography/tandem mass spectrometry), at 24 weeks post-ART initiation and study enrolment. Participant visits are considered to be at 24 weeks if between 154 and 196 days from enrolment.

2) Primary Outcome at 72 weeks post-enrollment. Composite measure of HIV VL suppression and retention in care at study clinic (binary) at 72 weeks post study enrolment, where VL suppression is defined as HIV VL <200 copies/mL by a standard lab-based assay on blood collected 68-84 weeks post-enrollment; and retention in care is defined as collecting ART at 68-80 weeks post-enrolment, at the study clinic or at a community pick-up point under supervision of the study clinic or pick-up at an ANC clinic, for women referred to ANC clinics during the study. The longer window for VL ascertainment is because we expect that a few participants who do not return in the window for retention in care, (i.e., 68-80 weeks), may have collected ART from a community pickup point or ANC clinic within 68-80 weeks. Therefore, there is an additional window from 80-84 weeks in which the study team will attempt to bring in the participant and obtain a viral load. If any participant has more than one viral load measurement obtained on blood within 68-84 weeks, the one closest to 72 weeks will be used.

   Participants who are either retained but not virally suppressed, or who are virally suppressed but not retained, do not achieve the endpoint. If a participant returns at 68-84 weeks and is determined to have picked up ART, but the team is unable to obtain blood for a viral load test, then the participant would be considered to be retained in care, but as viral load would be unavailable, the combined outcome would be considered missing. While our power calculations do not account for this source of missing data, we expect an extremely small number of participants, if any, will return to the clinic and not provide blood.

   To ensure unblinded determination of this primary endpoint, an adjudication committee will be formed to review available data for any participants reporting picking up ART elsewhere than the study clinic. The study CRFs record relevant longitudinal information such as referral to ANC or to community pickup and, for those not picking up ART at the study clinic, the participant's self-reported ART pickup. The study team's determination as to whether the participant is considered retained in care is also recorded. However, because the study team is not blinded to randomized group, the committee members will review the available data without access to randomized group, and their final determinations will be compared to existing determinations performed by the study team. Any discrepancies will be corrected to match the adjudication committee's decision.

7.2 Secondary Outcomes

Secondary outcomes for the trial include the following outcomes for statistical analysis:

- Composite measure of HIV VL suppression and retention in care at study clinic at 24 weeks post-enrolment (binary), with VL suppression defined as HIV VL <200 copies/mL by a standard lab-based assay; and retention in care defined as collecting ART during the 24-week visit at the study clinic, or at an ANC clinic, for those referred to ANC. Retention in care will be adjudicated in the same unblinded manner as at 72 weeks.

- TFV-DP concentration in DBS (continuous) at 72 weeks after study enrolment, considered to include 68-84 weeks post-enrolment, to allow VL and TFV-DP testing for those brought back after having missed the 72-week visit window.

7.3 Tertiary Outcomes

Process and intermediary clinical outcomes will include the following

a) Number of clinic visits
b) Time to VL results
c) Time to adherence counselling
d) Time to repeat VL in people with viraemia
e) Proportion in CCMDD
f) Proportion with drug resistance

Exploratory outcomes may include the following

a) TFV concentration in urine (at 24 and 72 weeks)
b) TFV concentration in hair (at 24 and 72 weeks)
c) Number eligible for CCMDD (during study follow-up)
d) Detection of HIV genotypic resistance (at 24 and 72 weeks)
e) Detection of HIV phenotypic resistance (at 24 and 72 weeks)
f) Viral re-suppression following prior viral failure (between 24 and 72 weeks)
g) Depression (at 24 and 72 weeks)
h) Sexual behaviors (at 24 and 72 weeks)
i) Self-reported ART adherence (at 24 and 72 weeks)
j) HIV stigma (at 24 and 72 weeks)
k) Intimate partner violence (at 24 and 72 weeks)
l) Substance use (at 24 and 72 weeks)

8 Primary exposure definition

In keeping with intention-to-treat analysis principles, the primary exposure of interest is randomization group as determined by the appropriate random allocation list(s). Even if a participant is mistakenly given the incorrect group assignment in implementing the study, they will be analyzed in the group to which they were randomly assigned according to the appropriate random allocation list. Using the random allocation assignment will avoid any actual or appearance of potential selection bias in the comparison groups, but could bias trial results towards the null when such errors are made. All efforts should be made to avoid such errors.

9 COVID-19

This study started on February 4, 2021 and included periods during COVID-19 pandemic lockdowns. Providers of critical health services and the study clinics have remained open throughout, but the pandemic slowed enrollment into the study, and may reduce some patients' ability to access transport to the clinic during lockdown periods. However, our study is a parallel randomized trial and arm was randomly assigned; COVID lockdown periods would not confound our comparisons, as we would expect both arms to be affected by COVID periods equally. However, it's possible that COVID periods could impact patients' ability to attend visits, access the intervention being tested, and get the benefit. Planned tables describing attendance to visits and receipt of POC tests for intervention group participants will provide insight on this question.

10 Statistical considerations

The following conventions will be followed for statistical reporting

1) Summary statistics will be median (Q1, Q3) and mean (SD) for continuous and count variables, and N (%) for categorical variables unless otherwise specified.
2) P-values will be two-sided and considered statistically significant at $\alpha=0.05$ unless otherwise specified
3) Statistical model results will be reported as point estimate, 95% confidence interval (CI) and associated p-value.
4) Whenever possible, statistical model results will be accompanied by summary statistics by relevant group in order to support contextualizing the results.

11 Interim analysis plan

For this study of implementation of ART care, there are no stopping rules in place, and we will not conduct interim efficacy analyses for either of the co-primary endpoints.

12 Multiple testing

The analyses of the two co-primary outcomes in the study answer separate research questions; the 24-week TFV-DP comparison will address whether providing monthly POC TFV adherence testing for the first five months following ART initiation supports better adherence, while the 72-week retention-in-care and viral suppression comparison addresses whether using monthly POC TFV adherence testing in the first five months followed by six-monthly POC VL testing, supports better long-term outcomes. With this in mind, we will not adjust either comparison for multiple testing but will interpret each result in the context of the other.

13 Missing Data

Where TFV-DP concentrations are missing due to being found to be below the lower limit of quantification or being undetectable, then they will be imputed as half the lower limit of quantification. The proportion of enrolled participants who are missing TFV-DP results entirely will be described (i.e., the proportion not contributing to the analysis). If rates of missing TFV-DP concentrations differ between arms, we will summarize the reasons for missingness and interpret the results of the analysis accordingly.

We expect little missing data for our co-primary outcome of viral suppression and retained in care because those not returning to pick up ART between 68-84 weeks by definition do not achieve the outcome and will therefore contribute to the analysis. Missing VL measurements for other reasons is expected to be rare. If rates of missing the composite endpoint data differ between arms, we will summarize the reasons for missingness and interpret the results of our analysis accordingly.

All efforts should be made to avoid missing data for reasons other than TFV-DP being undetectable, particularly for the co-primary outcomes.

14 Planned Statistical Analyses

14.1 CONSORT diagram

Screening and enrollment into the study will be shown in a CONSORT-style diagram, with summary of reasons for ineligibility or non-enrollment; randomization assignment into the two groups, and retention to the 24-week and 72-week (including up to 84 weeks) outcome assessment visits described.

14.2 Baseline Demographics

Baseline characteristics of enrolled participants will be summarized by randomization group, and overall, in a table. Baseline characteristics to include in the table are detailed in the table shell provided in Appendix I.

14.3 Efficacy Analyses

Twenty-four week outcome analyses will be conducted after all participants have passed the target visit window for the 24-week endpoint but before all participants have reached the 72-week endpoint. Seventy-two week analyses will be conducted at the end of the study.

All efficacy analyses will be performed using the intention-to-treat method in the sense that randomly assigned group will be our exposure regardless of adherence to POC testing offered. In addition, for our combined ART care outcome, we have designed the outcome to minimize missing data for our primary comparisons.

14.3.1 Co-Primary Outcome of TFV-DP concentrations at 24 weeks

Descriptive Analyses:

We will present summary statistics for TFV-DP concentrations at 24 weeks, as mean (SD) and median (IQR) concentration by randomized group. If not all participants have a detectable TFV-DP concentration, N (%) with detectable concentration will also be reported, and undetectable

drug level results will be imputed as described in section 12, Missing data. Missingness by arm will also be described as per section 12, missing data.

Inferential Analyses:
To test whether ART adherence differs between POC TFV adherence testing and standard-of-care (no adherence testing), we will conduct a complete-case analysis to compare mean TFV-DP levels between the intervention and standard-of-care groups using a two-sample t-test assuming equal variances. If we find that the data more closely resembles a log normal distribution than a normal distribution, we will log transform the data before making the comparison. While we expect randomization to produce comparable baseline groups, we will perform a secondary analysis to estimate adjusted differences in means using a multivariable linear regression model adjusted for key baseline variables, specifically sex, body mass index, hemoglobin, and creatinine clearance, which may influence DBS TFV-DP concentrations.

14.3.2 Co-Primary Outcome of virally suppressed and retained in care at 72 weeks

Descriptive Analyses:
We will present summary statistics for the combination of viral suppression and retained in care at 72 weeks, by randomized group. We will also present summary statistics for the component measures of retained in care at 72 weeks, and for VL suppression (as a complete case analysis among those with VL measure at 72 weeks). We will provide details on when we consider someone not retained in care because we could not reach them to assess retention before 84 weeks, vs we reached them and ascertained they had not picked up ART in the correct window. We will provide detail on the number retained due to picking up ART at a community pick-up point, and number picking up at an ANC clinic.

Inferential Analyses:
To test whether VS and retention in care at 72 weeks differs between POC TFV adherence testing followed by POC VL testing versus SoC (no adherence testing and lab-based VL testing), we will compare VS and retained in care using complete-case analysis to estimate the relative risk (RR) of having achieved the outcome in the intervention arm relative to the control arm using Poisson regression with robust standard errors, which provides unbiased estimates of the log RRs, while correcting standard errors for the choice of Poisson distribution. We will present the RR, two-sided 95% CI and p-value. While we expect randomization will provide us with comparable baseline groups, we will perform a secondary analysis to estimate adjusted RRs using a multivariable modified Poisson regression model adjusted for key baseline variables that would be expected to be strongly related to retention in care and/or viral suppression, specifically, baseline viral load and CD4 count.

14.3.3 Effect modification analyses

We will estimate the effect of the intervention within the following baseline subgroups

- TB co-infection at baseline (yes or no/not known)
- Gender (Men or women)
- Age >35 years or age ≤35 years
- Enrollment at urban clinic (ECRS) or rural clinic (Vulindlela)
- Evidence of undisclosed ART exposure (e.g. baseline viral suppression or baseline detectable ARV drug levels, if available)

We will also estimate outcomes separately within values of the following time varying covariates:

- Pregnant women and non-pregnant women (ever during study, prior to the visit)
- Enrolled in CCMDD and not enrolled in CCMDD (ever during study, prior to the visit)

Descriptive Analyses:
For each co-primary outcome, we will present summary statistics by randomized group by the value of each baseline subgroup variable. For each time-varying covariate, we will present summary statistics for the co-primary outcome at 72 weeks by the value of the covariate at 72 weeks.

Inferential Analyses:
For each co-primary outcome, for each subgroup variable, we will estimate the effect of the intervention within values of the subgroup variable using the same statistical model as the primary analysis but with the subgroup variable and interaction term between subgroup variable and randomization group added to the model. The subgroup-specific effect estimate will be reported from the model as well as the interaction term p-value representing the strength of the evidence for effect modification by the subgroup variable. Analysis of each time-varying covariate will be conducted in the same manner, but interpretation will take into account the fact that the covariate represents a post-randomization event and the resulting groups compared may not be comparable by arm.

14.4 Secondary outcomes

The secondary outcomes of (1) a combined measure of viral suppression and retention in care at 24 weeks and (2) ART adherence at 72 weeks, will be analyzed using the same methods as the corresponding co-primary outcomes, except that at 24 weeks, retained in care will be defined only as picking up ART at study clinic at 24 weeks; anyone missing the visit will be considered not retained.

14.5 Fidelity to the intervention

Descriptive Analyses:
Summary statistics will be provided for data from point-of-care TFV adherence testing from months 1-5 in a table to demonstrate how well the study was able to implement POC adherence testing in the intervention group. This table will augment reporting of the 24-week adherence co-primary result. This table will include the following data for weeks 4 to 20:

- POC TFV tests administered (among participants in the intervention arm attending a visit)
- Detectable POC TFV test results (among tests administered)
- Enhanced adherence counselling (EAC) provided (among participants with undetectable POC TFV test results)

Similarly, POC viral load testing data at 24- and 48-weeks will be provided in a table to demonstrate how well the study was able to implement POC VL testing. Data on completeness of POC viral load testing will be included. This table will augment reporting of the 72-week ART care co-primary result. This table will include the following process outcomes for weeks 24 and 48:

- POC viral load tests administered (among participants in the intervention arm attending a visit)

14.6 Process and intermediary clinical outcomes

Descriptive Analyses:
Process and intermediary clinical outcomes will be summarized by randomized group. Key process and intermediary clinical outcomes are listed in section 7.4, and below. Further process and intermediary outcomes are listed in the table shell in Appendix A to the SAP.

a) Number of clinic visits
b) Time to VL results
c) Time to EAC
d) Time to repeat VL in people with viraemia
e) Proportion in CCMDD
f) Proportion with drug resistance

Statistical inference:

We will formally statistically compare d) time to repeat VL in people with viraemia, and e), proportion in CCMDD, by randomized group. Each is dependent on other factors besides the intervention mechanics alone, and will be compared to see if improvement was achieved. We will not make statistical comparisons of the process outcomes of number of visits, time to viral load results, or time to EAC, because they are expected to be different by design of the intervention. In these cases, statistical significance between groups is insufficient to show the intervention had the expected effect -- it is a pretty low bar, because even if the intervention was implemented poorly or inconsistently, it's likely that the p-value comparing these outcomes in the intervention group vs. the control group would be statistically significant. Descriptive statistics for these outcomes will better indicate whether the intervention arm processes worked as expected. The proportion with drug resistance will likely be available only in the intervention group, and thus will only have descriptive statistics presented.

Formal statistical comparisons by randomized group, when performed, will be conducted as follows: for the binary outcome of proportion in CCMDD, we will report relative risks (RRs) from Poisson regression modified for relative risk regression by using robust standard errors (Zou, 2004); for time-to-event outcome of time to repeat VL in people with viraemia, we will report hazard ratios (HRs) from Cox regression. P-values and 95% confidence intervals will also be reported. If any participant has more than one incident of viraemia, we will use the Anderssen-Gill extension to the Cox model to incorporate multiple time-to-event outcomes per person.

14.7 Medical events

We will describe deaths and hospitalizations by randomized group.

14.8 Exploratory analyses

We may also compare the exploratory outcomes by randomized group. Formal statistical comparisons of these outcomes by randomized group will be conducted as follows: for count outcomes, we will report incidence rate ratios (IRRs) from Poisson regression; for binary outcomes, we will report relative risks (RRs) from Poisson regression modified for relative risk regression by using robust standard errors; for time-to-event outcomes, we will report hazard ratios (HRs) from Cox regression. P-values and 95% confidence intervals will also be reported. For repeated measurement binary and time-to-event outcomes (i.e., when these are per-visit level outcomes rather than per-participant level outcomes), comparisons will incorporate appropriate methods to adjust standard errors for correlation in outcomes within the same participant. For binary outcomes, the modified Poisson regression adjusts standard errors not only for the use of

Poisson errors instead of binomial, but also for repeated measurements (Yelland 2011). For time-to-event outcomes, we will use the Anderssen-Gill extension to the Cox model to incorporate multiple time-to-event outcomes per person.

15 References

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