VITAL STATISTICAL ANALYSIS PLAN

This Statistical analysis plan (SAP) follows Gamble et al (1).

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1. Administrative information

1.1. Title and trial registration

Assessment of a viral load result-driven automated differentiated service delivery model for participants taking antiretroviral therapy in Lesotho: Viral load triggered ART care in Lesotho (VITAL)

ClinicalTrials.gov, NCT04527874, registered on 27 August 2020

1.2. SAP version

V1.0, dated 2 September 2024

This SAP lays out the planned primary statistical analyses that look at the clinical effectiveness of the VITAL model of care within the VITAL trial.

1.3. Protocol version

V4, dated 23 July 2023

1.4. SAP revisions

Version	Date	Justification for each SAP revision	Timing of SAP revision in relation to study
1.0			

1.5. Roles and responsibilities

Name	Affiliation	Role
Nadine Tschumi	- Division of Clinical Epidemiology, Department of Clinical Research, University Hospital Basel, Basel, Switzerland - University of Basel, Basel, Switzerland	Statistician, SAP author
Frédérique Chammartin	- Division of Clinical Epidemiology, Department of Clinical Research, University Hospital Basel, Basel, Switzerland - University of Basel, Basel, Switzerland	Senior statistician responsible
Niklaus Labhardt	- Division of Clinical Epidemiology, Department of Clinical Research, University Hospital Basel, Basel, Switzerland - University of Basel, Basel, Switzerland	Sponsor and Chief investigator

1.6. Signatures

Name	Date	Signature
Nadine Tschumi	02.09.2024 | 18:13 MESZ	DocuSigned by: Nadine Tschumi 5F8B667990FA4A9...
Frédérique Chammartin	03.09.2024 | 08:10 CEST	DocuSigned by: F. Chammartin 0E09BF2613A14B1...
Niklaus Labhardt	03.09.2024 | 08:16 MESZ	DocuSigned by: Niklaus Labhardt D61BC2E808E04F8...

2. Introduction

2.1. Background and rationale

To sustainably provide good quality HIV care to the increasing number of people with HIV receiving antiretroviral therapy (ART), care delivery should shift from a "one-size-fits-all" approach to differentiated care models. Reducing the frequency of clinic visits through multi-months distribution of ART among people with suppressed viral load (VL) and no other clinical problems could save time and transport cost of people with suppressed VL while reducing the workload at health care facilities. This may allow focusing on people with elevated VL and/or other clinical problems and could thereby improve clinical outcomes of people with HIV. The VITAL model of care thus automatically differentiates HIV care based on previous VL results while providing a broad range of preference-based eHealth support to participants and clinical decision support to health care providers.

2.2. Objectives

The **primary objective** is to assess if the proposed automated differentiated service delivery model (aDSDM) is at least non-inferior in the proportion of participants engaged in care and virally suppressed <50 copies/mL at 24 months (window: 16-28 months) follow-up (intention-to-treat (ITT) population)

The **secondary objectives** are:

- To test if the proposed automated differentiated service delivery model (aDSDM) is superior in the proportion of participants engaged in care and virally suppressed <50 copies/mL at 24 months (window: 16-28 months) follow-up (intention-to-treat (ITT) population); and
- To test if the proposed aDSDM is cost-effective if the intervention is found to be superior or cost-saving if the intervention is found to be non-inferior.

3. Study methods

3.1. Trial design

Full details of the trial are available in the published protocol (2).

VITAL is a multicenter, pragmatic, cluster-randomized, open-label, non-inferiority trial. The rationale for a cluster randomized design with clinics as clusters is to minimize the risk of cross-contamination between the study arms. Also, the pragmatic cluster-randomized design is the method of choice for the evaluation of the effect of a model of care on patient outcomes. The study is conducted at 18 clinics in two districts of Lesotho (Butha-Buthe, Mokhotlong).

3.2. Randomization

Randomization is done at cluster (clinics) level with a 1:1 allocation and stratified by district (Butha-Buthe vs Mokhotlong). To obtain consent and to maximize transparency and ownership from the clinics, randomization events involving representatives of all health facilities and the District Health Management Team were conducted in each district. For randomization, opaque, equally-sized and sealed envelopes containing the group allocation (control or intervention) were held in a typical Lesotho hat (Mokorotlo). An independent person randomized the allocation sequence by drawing from another typical Lesotho hat (Mokorotlo) an equally-sized and sealed envelopes containing the names of health facility representatives one after each other. According to this sequence health center representatives drew their arm allocation, which was disclosed only after all participants had drawn an envelope at very end of drawing event.

clinic	stratifictation factor district	allocation
Makhunoane	Butha-Buthe	control
Linakeng	Butha-Buthe	intervention
Tsime	Butha-Buthe	control
St. Peters	Butha-Buthe	control
St. Paul	Butha-Buthe	control
Boiketsiso	Butha-Buthe	intervention
Motete	Butha-Buthe	intervention
Rampai	Butha-Buthe	control
Ngoajane	Butha-Buthe	intervention
Muela	Butha-Buthe	intervention
Malefiloane	Mokhotlong	intervention
St. James	Mokhotlong	control
Moeketsane	Mokhotlong	control
Mapholaneng	Mokhotlong	intervention
Linakaneng	Mokhotlong	control
Molikaliko	Mokhotlong	intervention
Libibing	Mokhotlong	control
St Martins	Mokhotlong	intervention

Table 1. *Clinic allocation.*

3.3. Sample size

We calculated the sample size for the non-inferiority cluster randomized design which corresponds to an individually randomized design multiplied by a design effect (3–5). We will use odds ratios (ORs) to assess the effect of the intervention on our binary primary endpoint. An OR of 1 corresponds to no relative effect, an OR >1 to a positive relative and an OR <1 to a negative relative effect in the intervention versus control clusters. We aim at testing the null hypothesis H_0: OR ≤ margin of non-inferiority (NI) versus the alternative hypothesis H_1: OR > NI, where the rejection of the null

hypothesis implies non-inferiority. The NI margin for the OR of reaching our primary endpoint is set to 0.8 (see section **3.4**).

We estimated an intraclass correlation coefficient of 0.04 as the proportion of the variance explained by the cluster structure in our population and included the estimated mean cluster size and standard deviation to our design effect. Our desired type I error rate was chosen as 0.025. With 9 clusters in the intervention group and 9 clusters in the control group, we will have 85% power to detect a one-sided difference of >10% in the primary endpoint between the intervention and the control arm.

3.4. Framework

This is a non-inferiority trial. If non-inferiority of the primary endpoint is established, we will assess superiority.

We chose a NI margin for the odds ratio of reaching our primary endpoint of 0.8, i.e., if the lower bound of the one-sided 97.5% confidence interval for the adjusted odds ratio for the primary outcome exceeds 0.8, then our intervention is non-inferior to standard of care. On an absolute scale, this non-inferiority margin corresponds to a higher absolute probability of failing to reach the primary endpoint of 5% in the intervention compared to the control group, if 65% of participants in the control arm will be engaged in care with documented viral suppression at 24 months follow-up.

If the lower bound of the two-sided 95% confidence interval for the adjusted odds ratio for the primary endpoint exceeds 1.0, we will consider our intervention superior.

3.5. Statistical interim analyses and stopping guidance

No interim analyses are planned.

3.6. Timing of final analysis

All outcomes will be analysed collectively after the trial was closed, this SAP signed, and the data freezed.

3.7. Timing of outcomes assessment

Table 2 shows the nominal visit months, the permitted ranges according to the protocol, and the ranges that will be used for analysis.

Nominal visit month	Window according to the protocol in months	Range used for analysis
12	4-16 months	- Months will be analysed as calendar months, i.e., for a participant enrolled on 10.10.2020 the 24 months window will be 10.02.2022 -10.02.2023. - If multiple viral loads are available in the outcome window, the closest measurement to the nominal visit month will be considered for analysis.
24	16-28 months	

Table 2. *Nominal visits and permitted windows.*

4. Statistical principles

4.1. Confidence intervals and p-values

Statistical tests and 97.5% confidence intervals for non-inferiority comparisons will be one sided-sided. Statistical tests and 95% confidence intervals for superiority and equivalence comparisons will be two-sided. P-values will be presented where appropriate.

For the primary endpoint (non-inferiority and subsequently superiority testing) no statistical multiplicity adjustment will be needed because of the closed testing principle (6,7). If in the primary endpoint the intervention fulfills the non-inferiority criterion, secondary endpoints which may become the basis for additional claims will be evaluated hierarchically (8). Statistically significant effects in these secondary endpoints, which are part of our confirmatory strategy, could be considered for additional claims. Clinically relevant secondary endpoints are listed separately and will be evaluated independently of the result of the primary endpoint. They would require further investigation if significant differences were observed, but the primary objective has not been achieved. For the secondary endpoints expressing supportive evidence, no claims are intended, and only descriptive statistics will be presented.

4.2. Adherence and protocol deviations

Non-adherence to protocol procedure assessments according to ***Figure 1*** (SPIRIT diagram) are considered as protocol deviations and will be reported accordingly.

	Enrolment	Follow-up	Endpoints	
TIMEPOINT	***0***	***Individual schedule***	***12 months*** **	***24 months*** ***
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
INTERVENTIONS:				
Standard of care (control)	x----------x			
VITAL model of care	x----------x			
ASSESSMENTS:				
Screening	X			
Socio-demographic data / clinical history • Socio-demographic data • ART history • Comedication • Family planning/sexual health • Adherence to ART	X			
eHealth preferences* • Availability of cell-phone(s) and number(s) • Type, time and weekday of eHealth support	X	X		
Pharmacy refill (from ART card) • Number of ART / TB / TPT pills dispensed and next refill date	X	X		
Clinical assessment • Serious illness / hospitalization since last visit • Pregnancy / breastfeeding • Next VL due date • ART action taken / TPT action taken • Adherence to ART (if VL unsuppressed)* • Type of EAC (if VL unsuppressed)* • ART changes	X	X		
Mental health assessment • AUDIT-C, PT-PTSD, PHQ-9, GAD7, Druguse	X	X		
Viral load database review • Viral load results and dates • Treatment changes	X	X	X	X
Qualitative in-depth interview with a subset of participants		X		

Figure 1. SPIRIT figure for the schedule of enrolment, interventions, and assessments. The color code corresponds to the responsible person for the assessment or task: Brown: VITAL study team, blue: clinic staff, green: VITAL data management team, purple: other VITAL study team members.

TB: tuberculosis; TPT: tuberculosis preventive therapy; VL: viral load; EAC: enhanced adherence counselling; * in VITAL intervention clinics only; ** 12 months window; *** 24 months window: 16-18 months

4.3. Analysis populations

The VITAL trial asses a model of HIV care in a "real-world" setting. The main interest is to assess effectiveness of the VITAL intervention, i.e. the degree of effect under "real-world" conditions. Accordingly, the ITT population is the analysis population of most relevance. Therefore, in the primary analysis, we will analyse participant outcomes in the cluster they were enrolled in, independent of their follow-up. As a sensitivity analysis we will conduct a per-protocol analysis

includes participants for whom the VITAL intervention was technically successful defined as all viral loads available in the VITALapp ≤31 days after phlebotomy.

5. Trial population

5.1. Screening data

No specific screening data were captured, aside from those used to determine eligibility for the trial (see 5.2).

5.2. Eligibility

Full inclusion/exclusion criteria are as follows:

At **individual level**, inclusion criteria at enrolment for the VITAL trial are the following:

- taking ART;
- ≥ 18 years old;
- provided written informed consent;
- expressed the intention to remain at the same facility for the duration of the trial at enrollment; and
- not enrolled in another study judged as non-compatible by the (local) principal investigator.

At **cluster level**, the inclusion criteria for the VITAL trial are the following:

- nurse-led public or missionary clinic in the districts of Butha-Buthe and Mokhotlong;
- consent of clinic management (signed agreement with clinic management);
- access to the internet (internet connection must not be constant, but there must be possibility to down- and upload information daily); and
- the clinic sends plasma VL samples to Butha-Buthe government hospital laboratory for analysis.

Screening/eligibility data will be summarized in a CONSORT flowchart, showing the total number of clusters screened and the reasons for screening failures.

5.3. Recruitment

The CONSORT flowchart will display the numbers of clusters randomized by group. Further, the flowchart will include the numbers of participants screened and enrolled per cluster.

5.4. Withdrawal/follow-up

The CONSORT flowchart will summarize disengagement from care as well as reason for it (dead, hospitalized, transfer-out, stopped ART no information found after tracing) and study withdrawal, by group.

5.5. Baseline participant characteristics

Baseline participant characteristics will be summarized by group, using medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables. There will be no formal testing for baseline characteristics differences across randomized groups (9,10).

6. Analysis

Analyses will follow CONSORT guidelines, including extensions for non-inferiority trials (11,12). Analyses will include all follow-up to the date of data freeze; as well as documented and reasoned changes thereafter.

6.1. Outcome definitions

An overview of the primary and all secondary endpoints is given in ***Table 3***. For the primary endpoint, two hypotheses will be hierarchically tested:

1. non-inferiority in the ITT population; and
2. superiority in the ITT population.

Since the first approved protocol version and registration of the trial, the following amendments were made to the outcomes:

Change to the primary endpoint:

- In line with the national HIV treatment guideline of Lesotho update in 2022 and considering the detection threshold of 40 copies/mL of the increasingly used point-of-care viral load testing, the cutoff for viral suppression was raised from 20 copies/mL to 50 copies/mL.

Changes to secondary endpoints:

- In all secondary endpoints the cutoff of viral suppression was adapted to 50 copies/mL as for the primary endpoint.
- "Switch" considered as change of ART core agent was replaced by "ART regimen modification" since the nation-wide roll-out of dolutegravir in Lesotho led to a change of the guidelines when to switch to second-line due to ART failure and core agent changes became extremely rare among persons taking dolutegravir.

Secondary endpoints moved to different analyses/ manuscripts:

The following endpoints are unchanged but will be considered in separate analyses for separate manuscripts as they would go beyond the scope of the main manuscript.

- *"Proportion of participants requesting a VL result notification through SMS in intervention clusters"*
- *"Proportion of SMS delivered successfully in intervention clusters"*
- *"Proportion of participants using the call-back option through District ART Nurse in intervention clusters"*

- *"Proportion of participants screened positive for TB by automated call in intervention clusters"*

Dropped secondary endpoints:

- *"Proportion of participants appreciating the automated differentiated service deliver model in intervention clusters" was replaced by qualitative in-depth interviews with a subset of participants (already conducted).*
- *"Proportion of health care providers appreciating the automated differentiated service delivery model" was dropped for feasibility.*

Addition of sensitivity analyses:

- We added a sensitivity analysis for the primary endpoint using multiple imputation for VLs missing at 24 months in the ITT population.
- We added a sensitivity analysis for the primary endpoint in a per-protocol population including participants for whom all viral loads were available in the VITALapp ≤31 days after phlebotomy.

Primary endpoint	**Population**	**Comparison**
Proportion of participants engaged in care (defined as documented visit attendance) with documented viral suppression (**<50 copies/mL**) 24 months (16-28 months) after enrollment*	ITT	i. Non-inferiority ii. Superiority
Sensitivity analysis for the primary endpoint		
1. Proportion of participants engaged in care (defined as documented visit attendance) with documented viral suppression (**<1000 copies/mL**) 24 months (16-28 months) after enrollment	ITT	1.-3.: i. Non-inferiority ii. Superiority
2. Proportion of participants engaged in care (defined as documented visit attendance) with documented viral suppression (**<50 copies/mL**) 24 months (16-28 months) after enrollment	ITT using multiple imputation for VLs missing at 24 months	
3. Proportion of participants engaged in care (defined as documented visit attendance) with documented viral suppression (**<50 copies/mL**) 24 months (16-28 months) after enrollment	PP*	

Secondary endpoints which may become the basis for additional claims			
4.	Proportion of participants with viral re-suppression (**<50 copies/mL**) 24 months (16-28 months) after enrollment among all participants with an unsuppressed VL (≥ 50 copies/mL) during the first 12 months of follow-up	ITT	4.-5. hierarchical (i.e. 4. only if the primary endpoint is non-inferior, and 5. only if 4 is superior): Superiority
5.	Proportion of participants with sustained viral suppression (defined as >1 VL **<50 copies/mL**) during 24 months follow-up	ITT	
Secondary endpoints indicative of clinical benefit or harm			
6.	Rate of mortality at 12 and 24 months after enrollment	ITT	6.-7.: Equivalence 8.: Superiority
7.	Proportion of participants with confirmed TB diagnosis at 12 and 24 months after enrollment		
8.	Disengagement from care at 12 and 24 months after enrollment		
Secondary endpoints expressing supportive evidence			
9.	Time to follow-up VL in case of an unsuppressed VL (≥ 50 copies/mL)	ITT	9.-13.: Superiority (for 9.-11. the upper bound of the 95% CI must be below 1, and for 12.-13. the lower bound of the 95% CI must be above 1)
10.	Time to ART regimen adaption in case of virologic failure**		
11.	Rate of clinic visits at 24 months after enrollment		
12.	Proportion of participants with ART regimen modification due to virologic failure at 12 and 24 months among participants with virologic failure**		
13.	Proportion of participants having received a course of TPT		

Table 3. Primary and secondary endpoints as well as sensitivity analyses. **The per-protocol analysis includes participants for whom all viral loads were available in the VITALapp ≤31 days after phlebotomy. **Virologic failure is defined according to the implementation in VITAL, i.e. two consecutive VLs ≥1'000 copies/mL or three consecutive VLs ≥20 copies/mL from VITAL start - 22.12.2022 and two consecutive VLs ≥50 copies/mL from 23.12.2022 – VITAL closure.*

6.2. Analysis methods

General: Continuous variables will be inspected using histograms: 1) to assess for outliers which may be queried for accuracy, and 2) to assess whether appropriate transformations are required for the regression model. Outcomes will be summarized using medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables, by randomized group.

Percentages will be reported to one decimal place. For all regression models we will report adjusted odds ratios and adjusted risk differences. If any model should not converge using the identity link (to estimate the adjusted risk difference), only the adjusted odds ratios will be reported. We will consider the day of enrolment until the day of primary endpoint VL or until 28 months after enrolment if endpoint VL missing as study period for each participant.

Primary outcome: For the analysis of the primary outcome, we will use a multi-level logistic regression model including clinic cluster as a random effect, arm allocation and the randomization stratification factor (district) as a fixed effect. Unavailability of a viral load or only an invalid viral load result in the predefined primary endpoint window (for any reason) will be considered as failure. Results will be reported as adjusted odds ratios and absolute differences with confidence intervals. For the primary endpoint, non-inferiority in the ITT population and superiority in ITT will be assessed but no statistical multiplicity adjustment will be needed because of the closed testing principle. For the non-inferiority comparison, a confidence interval approach will be used. Under the assumptions of the sample size calculation, non-inferiority is compatible with the lower bound of the one-sided 97.5% confidence interval for the adjusted odds ratio for the primary outcome exceeding 0.8. A figure illustrating the confidence interval and the non-inferiority margin will be presented. If the non-inferiority is established, then we will assess for superiority by assessing whether the two-sided 95% confidence interval of the adjusted odds ratio excludes 1.

Assessment of cost (primary outcome): We will analyse cost-effectiveness if the intervention is found to be superior or assess the budget impact if the intervention is found to be non-inferior. For the cost-effectiveness analysis, we will use the primary endpoint and mathematical models of HIV transmission. Costing data will include: (1) conversion rate of local currency to U.S. dollars at 6-month intervals over the life of the project; (2) costs of all commodities used in the intervention; (3) average time clients spent with intervention including transportation, (4) staff time and representative salaries; (5) local average wages of the target population; (6) remunerations to clinics; and (7) other relevant costs, including training of providers and transport costs.

Time and motion studies are conducted to collect the costing data necessary to provide the intervention. All clinics contributed several time and motion observations. An experienced research assistant collects data on time required to complete each step of the intervention. Observing multiple visits allows estimation of the average time taken for each step. The time taken for research purposes (e.g. data collection) is noted separately from the estimated time needed for clinical services. In addition, interviews with study staff to quantify the effort required for each step of the intervention are conducted, as well as interviews with participants to assess opportunity costs. We also ask participants what expenses and opportunity costs they incurred while receiving the intervention. Furthermore, we collect data on the average cost of medical care in Lesotho associated with HIV infection and AIDS through literature review. A discount rate of 3% is used with sensitivity analysis of 0% to 5%.

Sensitivity analyses (primary outcome):

1. **Proportion of participants engaged in care (defined as documented visit attendance) with documented viral suppression (<1000 copies/mL) 24 months (16-28 months) after enrolment:** The first sensitivity analysis assesses the robustness of the primary analysis to the primary endpoint definition by repeating the primary outcome analysis (ITT) with a VL cutoff modified to 1’000 copies/mL.

2. **Proportion of participants engaged in care (defined as documented visit attendance) with documented viral suppression (<50 copies/mL) 24 months (16-28 months) after enrolment:** The second sensitivity analysis assesses the robustness of the primary analysis to the primary endpoint definition by repeating the primary outcome analysis (ITT) with imputing the VLs of participants who were engaged in care but do not have a documented viral load at 24 months using the viral load history of the participants.
3. **Proportion of participants engaged in care (defined as documented visit attendance) with documented viral suppression (<50 copies/mL) 24 months (16-28 months) after enrolment:** The third sensitivity analysis assesses the robustness of the primary analysis to technical challenges with viral load result availability by repeating the primary outcome analysis in the per-protocol population defined as participants for whom all VL results were available in the VITALapp ≤31 days after phlebotomy during the study period.

Effect modification (primary outcome): For effect modification of the primary outcome the following variables will be considered:

i. Age groups (18-24, 25-39, 40-59, and ≥60 years)
ii. Gender (female, male)
iii. Cell phone access (yes, no)

Analyses will be performed as for the main primary outcome analysis including an interaction term between these potential effect modifiers and the randomized group. If an interaction term is found to be significant (p-value<0.05), effect estimates will be summarized descriptively by subgroup categories. As the study is not powered for these pre-planned subgroup analyses, no formal hypothesis testing will be done.

Secondary endpoints which may become the basis for additional claims: In case non-inferiority of the primary endpoint is established, these will be evaluated hierarchically.

1. **Proportion of participants with viral re-suppression (<50 copies/mL) 24 months (16-28 months) after enrollment among all participants with an unsuppressed VL (≥ 50 copies/mL) during the first 12 months of follow-up:** This analysis will include individuals with a VL ≥50 copies/mL in the first 12 study months and then directly follow the primary endpoint analysis.
2. **Proportion of participants with sustained viral suppression (defined as >1 VL <50 copies/mL) during 24 months follow-up:** This analysis will directly follow the primary endpoint analysis with endpoint adapted to sustained viral suppression <50 copies/mL throughout the study. Sustained viral suppression is defined as >1 VL <50 copies/mL from study start to end of 24-month window (0-28 months) along with no VL ≥50 copies/mL.

Secondary endpoints indicative of clinical benefit or harm: These will be evaluated independently of the primary objective and without hierarchy / multiplicity adjustment.

3. **Rate of mortality at 12 and 24 months after enrollment:** This analysis will use Cox regression adjusted for clinic and district by study arm.
4. **Proportion of participants with confirmed TB diagnosis at 12 and 24 months after enrollment:** This analysis will directly follow the primary endpoint analysis with endpoint TB diagnosis (window: 0 months to primary endpoint or 28 months).

5. **Disengagement from care at 12 and 24 months after enrollment:** This analysis will directly follow the primary endpoint analysis with endpoint disengagement from care at 24 months, defined as neither a documented visit attendance nor a VL measurement (window: 16-28 months).

Secondary endpoints expressing supportive evidence:

6. **Time to follow-up VL in case of an unsuppressed VL (≥ 50 copies/mL):** This analysis will consider the time in weeks to follow-up VL in case of an unsuppressed VL (≥ 50 copies/mL) as outcome and use a multi-level linear regression model including clinic cluster as a random effect, arm allocation and the randomization stratification factor (district) as a fixed effect.
7. **Time to ART regimen adaption in case of virologic failure:** This analysis will consider the time in weeks to ART regimen adaption in case of virologic failure (defined as two consecutive VLs ≥1'000 copies/mL or three consecutive VLs ≥20 copies/mL from VITAL start - 22.12.2022 and two consecutive VLs ≥50 copies/mL from 23.12.2022 – VITAL closure) as outcome and use a multi-level linear regression model including clinic cluster as a random effect, arm allocation and the randomization stratification factor (district) as a fixed effect.
8. **Rate of clinic visits at 24 months after enrollment:** This analysis will consider the number of clinic visits throughout the study period as outcome and use and use a multi-level Poisson regression model with offset study duration including clinic cluster as a random effect, arm allocation and the randomization stratification factor (district) as a fixed effect.
9. **Proportion of participants with ART regimen modification due to virologic failure at 12 and 24 months among participants with virologic failure:** This analysis will only include people with a virologic failure (defined as two consecutive VLs ≥1'000 copies/mL or three consecutive VLs ≥20 copies/mL from VITAL start - 22.12.2022 and two consecutive VLs ≥50 copies/mL from 23.12.2022 – VITAL closure). Then, this analysis will directly follow the primary endpoint analysis with endpoint ART modification.
10. **Proportion of participants having received a course of TPT:** This analysis will directly follow the primary endpoint analysis with endpoint having received a course of TPT throughout the study period.

6.3. Missing data

Where applicable, percentages will be of non-missing values, with the number (%) of missing values reported separately.

As detailed in section **6.2**, main analyses of the primary outcome will include all participants as randomized with missing data counted as failures. No missing covariates are expected as the analysis only includes arm, stratification factor district and cluster. There will be a sensitivity analysis assessing the effect of imputing missing viral loads in the primary endpoint window.

6.4. Additional analyses

6.5. Harms

Safety data are included as the following secondary endpoints (section **6.2**):

- Rate of mortality at 12 and 24 months after enrollment

- Proportion of participants with confirmed TB diagnosis at 12 and 24 months after enrollment

- Disengagement from care at 12 and 24 months after enrollment

6.6. Statistical software

All analyses will be performed using the latest version of the statistical software R.

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