Same-day versus rapid ART initiation in HIV-positive individuals presenting with symptoms of tuberculosis: an open-label randomized non-inferiority trial in Lesotho and Blantyre district, Malawi

STATISTICAL ANALYSIS PLAN

Trial registration: NCT05452616

Protocol version 1.3.1, 29 May 2023

SAP version 2.0, 14 January 2025

(Statistical analysis plan drafted following Gamble et al (1))

1. Administrative information

Revision history

Version	Date	Who	Comments
0.1	30 May 2024	Tracy Glass	First draft
0.2	20 June 2024	Tracy Glass	Revised to include feedback from core SaDAPT team plus to add estimand framework.
0.3	24 June 2024	Tracy Glass	Revised to incorporate feedback of team and receive estimand input from external reviewer.
1.0	27 June 2024	Tracy Glass	Incorporates all feedback of team and estimand input from external reviewer. For signature.
1.1	13 January 2025	Tracy Glass	Corrects small inconsistencies. Clarifies the detection limit used for the primary analysis for devices in Malawi with higher VL detection limit than 400 copies/mL.
2.0	14 January 2025	Tracy Glass	For signature.

Roles and responsibilities

Name	Affiliation	Role
Tracy Glass	Swiss TPH, Switzerland	Trial statistician
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Signatures

Name	Signature	Date
Tracy Glass	DocuSigned by: 38DF88AA385F454...	15-Jan-2025 | 11:16:45 CET
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Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
CNS	Central nervous system
CrAg	Cryptococcal antigen
CRF	Case report form
DBS	Dried blood spot
HIV	Human immunodeficiency virus
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRIS	Immune reconstitution inflammatory syndrome
ITT	Intention to treat (analysis population)
PLHIV	People living with HIV
PP	Per protocol
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
SDI	Same-day initiation
Swiss TPH	Swiss Tropical and Public Health Institute
TB	Tuberculosis
TPT	TB preventive treatment
VL	Viral load
WHO	World health organization
W4SS	WHO four-symptom screening

Data management and sharing

Data are captured by study staff directly into an electronic RedCap database, hosted at University of Basel. Data export is done regularly by the study data manager. Queries are raised by the data management, statistics, and monitoring teams and resolved by the site teams.

Key trial data will be made available just before publication of the main manuscript through an appropriate data repository such as Zenodo, and will be referenced accordingly in the main manuscript.

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2. Introduction

2.1 Background and rationale

HIV remains a major cause of morbidity and premature death in many sub-Saharan African countries including Lesotho and Malawi. The most important opportunistic infection associated with HIV is TB, accounting for over 200'000 HIV-related deaths worldwide, mainly in low-income settings, where prevalence of HIV/TB-coinfection is highest.

An important approach to improve access to ART—and thereby reduce HIV transmission as well as AIDS related morbidity and mortality—is the implementation of rapid, and if possible same-day initiation (SDI) of ART. PLHIV with opportunistic infections are at risk of developing immune reconstitution inflammatory syndrome (IRIS) after initiation of ART. Until the release of a guideline update in 2021, WHO had recommended to delay initiation of ART in case of presumptive TB until TB has been investigated and TB treatment initiated if TB disease has been confirmed in order to reduce the risk of IRIS. The 2021 guideline update contains for the first time a "clinical consideration" to start ART in PLHIV with presumptive TB but no signs of central nervous system (CNS) disease while rapidly investigating for TB, thus allowing SDI for this subgroup of PLHIV. The guidelines emphasize the need for further research on the impact of SDI in PLHIV with presumptive TB on various health outcomes including mortality, HIV and TB outcomes, retention in care, adverse events and IRIS.

2.2 Objectives

To compare two approaches for the timing of ART initiation in PLHIV with presumptive TB but no signs of CNS disease ("ART first" versus "TB results first") with regard to HIV viral suppression, engagement in care, serious adverse events (SAEs) and adverse events (AEs) consistent with TB-IRIS (AEs of special interest, AESIs) in a randomized trial reflecting routine primary and secondary care setting in Lesotho and Malawi .

Primary objective: To assess if same-day ART initiation ("ART first") is non-inferior to rapid ART initiation ("TB results first") with regard to HIV viral suppression (VL <400 copies/mL) 26 weeks after enrolment among PLHIV with presumptive TB

Secondary objectives: To compare in PLHIV with presumptive TB same-day ART initiation ("ART first") versus rapid ART initiation ("TB results first") with regard to:

- retention in care
- disengagement from care
- unsuppressed VL
- safety outcomes (SAEs, and AESIs)
- TB incidence
- proportion of PLHIV with rapid ART initiation (within 7 and within 28 days)

Exploratory objectives:

- To describe the prevalence of TB disease at enrolment

- To assess potential sociodemographic and clinical risk factors for adverse outcomes after same day or rapid ART initiation
- To assess HIV phylogenetics and resistance at enrolment

3. Study methods

3.1 Trial design

This is an open-label, two country, two-arm, parallel-group 1:1 individually randomized controlled trial, conducted in Lesotho (7 facilities) and Blantyre district of Malawi (4 facilities). Full details of the trial design are available in the published protocol (2).

Trial population

Participants were recruited among individuals presenting at one of the study clinics. Routine staff of all study clinics were asked to identify individuals, 12 years or older, testing HIV-positive or known to be HIV-positive and not taking ART to the trial's site investigator. The site investigator then screened potentially eligible individuals based on the below-mentioned inclusion and exclusion criteria and approach them for consent.

Inclusion criteria are:

- 12 years or older
- HIV-positive
- Not taking ART (naïve or reported no ART intake since 90 days or more)
- Presenting with one or more TB symptoms according to WHO four-symptom screening (4WSS: reported cough, fever, weight loss, night sweats)
- Planning to continue care at the study facility for at least 30 weeks
- Consent (age 18 years or older) or assent and guardian consent (age 12 - 17 years)

Exclusion criteria are:

- Medical condition requiring admission or referral to a higher level health facility at enrolment
- Symptoms or clinical signs suggestive for diseases of the central nervous system (CNS)
- Positive cryptococcal antigen test (CrAg)
- Reporting to be pregnant (pregnancy test not required)
- Taking TB treatment or TB preventive therapy (TPT)

Trial procedures

Participants were consecutively enrolled and randomized in the ratio 1:1. Participants were recruited among individuals presenting at one of the primary and secondary level study clinics. All participants provided written informed consent. Enrolled participants received a clinical evaluation including an interview and physical examination, and laboratory tests, in particular diagnostic tests for TB. A follow-up study visit is expected to be done 26 weeks after enrolment. Further details are provided in the protocol (2).

Trial arms

The two arms of the trial are in brief:

"ART first" arm:
- Offer of ART initiation on the day of enrolment independent of TB investigations

"TB results first" arm:
- Offer of ART initiation only after active TB has been refuted or confirmed

Further information about procedures for the trial arms can be found in the protocol (2).

Endpoints

As per the protocol, the primary endpoint of the trial is:

- HIV viral suppression <400 copies/mL 26 (22 – 40) weeks after enrolment (obtained from routine laboratory reports at study facility, from laboratory reports of referral facility in case of transfer out, or from dried blood spot (DBS) sample for participants without documented clinic visit but found during home visit tracing)

As per the protocol, the secondary endpoints of the trial are:

- Retention in care 26 (22 – 30) weeks after enrolment, defined as a documented ART clinic visit between 22 and 30 weeks after enrolment
- Engagement in care 26 (22 – 30) weeks after enrolment, defined as reporting regular ART intake, irrespective if a documented visit took place between 22 and 30 weeks after enrolment
- Disengagement from care 26 (22 – 30) weeks after enrolment, defined as non-engaged in care but reached through patient tracing
- Lost to follow-up 26 (22 – 30) weeks after enrolment, defined as non-retained in care and not reached through tracing
- Non-traumatic mortality, SAEs, and AESIs (see section 7.1.3 for definition) during the first 30 weeks after enrolment
- Incidence of TB disease (microbiologically confirmed and/or clinical diagnosis) during the first 30 weeks after enrolment, defined as any TB diagnosis after enrolment not classified as prevalent TB at enrolment (see definition below under exploratory endpoints)
- HIV viral suppression at 26 (22 – 40) weeks using different thresholds (<20 copies/mL; <100 copies/mL; <1000 copies/mL)
- ART initiation within 7 and within 28 days after enrolment

As per the protocol, the exploratory endpoints of the trial are:

- Clinical characteristics of participants with non-traumatic hospitalizations and deaths in PLHIV with presumptive TB
- Prevalence of active TB diagnosed at enrolment, defined as TB diagnosed clinically or microbiologically through the TB investigations initiated at enrolment and completed up to a maximum of 28 days after enrolment.

3.2 Randomization

Participants were randomly allocated to trial arms at the time of enrolment. Randomization was stratified by country (Malawi and Lesotho) with randomly varying block sizes (details on block sizes held by the trial statistician). The randomization lists were generated by computer by an independent statistician not involved in the trial and uploaded to the study database. Allocation was revealed to the study staff electronically on the study tablet. Study staff then informed routine staff about arm allocation.

3.3 Sample size

As per the protocol: The sample size has been calculated with regard to the primary endpoint of the study. Secondary endpoints were not considered for the determination of the sample size. The expected proportion with viral suppression at 26 weeks after enrolment in the "TB results first" arm is 75%.
To test the hypothesis of non-inferiority of the primary outcome between the two arms, we set the non-inferiority margin to 10%, the power to 80%, and a one-sided alpha level of 0.025. These assumptions yield a sample size of 295 participants per arm.

If participants were found to be ineligible post-randomization and before recruitment ended (primarily for TB investigations happening prior to enrolment), they were replaced in order to reach the required sample size of 295 eligible participants per arm. Additional participants found to be ineligible after randomization will be excluded without replacement. Female participants becoming pregnant after enrolment will not be excluded.

3.4 Framework

The primary endpoint comparison between the two arms is non-inferiority. If the intervention arm (ART first) is found to be non-inferior to the control (TB results first), in both the ITT and per-protocol population, then we will assess for superiority (see section 6.2).

3.5 Statistical interim analyses and stopping guidance

A data safety monitoring board (DSMB) was set up with the purpose to protect the safety of study participants, to assist and advise the SaDAPT steering committee to protect the integrity, validity and credibility of the trial. The main task of the DSMB is to review SAEs and AESIs. Based on the review of SAEs and AESIs, the DSMB members shall flag concerns regarding safety and give recommendations to the SaDAPT Steering Committee whether to continue, amend or halt the trial due to these concerns. The trial protocol does not foresee any interim analysis or interim review of outcome data. Further details are provided in the DSMB charter.

3.6 Timing of final analysis

Once the last participant has reached the endpoint or 40 weeks have passed since their randomization, the data will be cleaned. Once the database is considered complete, it

will be locked. The locked database will be stored at the Division of Clinical Epidemiology at the University Hospital Basel.

3.7 Timing of outcome assessments

Baseline is defined as the date of randomization. Time will be measured from randomization.

Baseline laboratory results are defined as those measured at the time of screening to a maximum of 14 days after screening. Of note, the time of a laboratory result is defined as the time when the sample was taken, not the time when the sample was processed or result available. Any laboratory tests done to establish a TB diagnosis and completed within 28 days of enrolment are considered for the establishment of prevalent TB.

Table 2 shows the nominal activity weeks and the permitted ranges as defined in the protocol, and as defined for analysis. The analysis windows are chosen to be as inclusive (wide) as possible while retaining clinical relevance, and without overlap between the windows for different activities. For the primary outcome and secondary outcomes of viral load, if there is more than one measurement recorded within the allowed time window, then any evidence of viral suppression within the window will be considered. For all other measurements and outcomes, if there is more than one measurement within a given interval, then the value will be taken that is within the protocol defined window but closest to the nominal activity day.

Table 1. Nominal activities and permitted windows.

Activity/endpoint	Nominal activity week	Nominal activity day	Protocol defined window, weeks	Protocol defined window, days
ART initiation	1	7	<1	<7
ART initiation	4	28	<4	<28
Study visit	26	182	22 - 30	154 - 210
TB Incidence	<30	<210	4 – 30	28 – 210
Safety events	<30	<210	0 - 30	0 - 210
Register review	>=30	>=210	>=30	>=210
Tracing	31-40		31 - 40	217 - 280
Primary outcome	22 - 40	154 - 280	22 – 40	154 – 280

4. Statistical principles

4.1 Confidence intervals and p-values

Statistical tests and confidence intervals will be two-sided. Estimates will be presented with 95% confidence intervals. P-values will be presented where appropriate. No adjustments will be made for multiple testing nor interim analyses. Interpretations will be based on the strength of evidence of effect size and consistency of results for related outcomes.

4.2 Adherence and protocol deviations

We are conducting a study attempting to reflect routine care with as little influence by the study activities as possible.

Deviations by routine clinical staff from procedures described in the protocol were not usually considered study deviations and did not affect the participant's retention in the trial. Participants not receiving their assigned intervention was not considered a safety risk, but was considered a protocol deviation.

Any protocol deviations as reported by the trial team or detected at the time of data cleaning or analysis will be described by arm.

4.3 Analysis populations

As per the protocol (2), all analyses will be done by the trial statistician using R (the R Foundation for Statistical Computing) or Stata (version 18, Stata Corporation, Austin/Texas, USA). Analysis will follow CONSORT guidelines. Primary analyses for the non-inferiority comparison will be performed on both the ITT and per protocol (PP) sets (3).

Our approaches for the primary outcome are further detailed in the context of the estimands framework in Tables 2a and 2b (4).

For secondary outcomes related to VL (achieving viral suppression defined by other thresholds), we will employ similar methods as for the primary outcome (both superiority and non-inferiority comparisons).

For the remaining secondary outcomes, we will employ similar methods as for the primary outcome but under the superiority comparison only.

Table 2a. Estimand framework: primary outcome for superiority comparisons, resembling intention to treat approach [1].

Estimand attribute	Definition	Comments
Population	Individuals aged 12 years or older, testing HIV-positive or known to be HIV-positive and not taking ART, with one or more TB symptoms according to WHO four-symptom screening (4WSS), who would not die from a trauma-related cause before having the endpoint measured.	Exclusion of individuals considered too ill to follow standard care (needing admission or referral, CNS symptoms, or a positive CrAg test), pregnant women, or those taking TB treatment were excluded as written in the protocol. Exclusion of individuals who die from trauma-related causes before having the endpoint measured.
Treatment conditions	Same day ART start ("ART first") vs. ART start once TB confirmed or refuted ("TB results first")	
Endpoint	HIV viral load measured and suppression <400 copies/mL 26 (22 – 40) weeks after enrolment and did not die from a non-trauma-related cause prior to 40 weeks.	Endpoint clarified to include those who die from a non-trauma-related cause or were LTFU without a VL measurement as "failures", i.e. did not achieve viral suppression.
Summary measure	Risk differences. We will also report odds ratios and risk ratios.	
Handling of intercurrent events (IE) [2]		
Ineligible	"Principal stratum" approach	Individuals found to be ineligible after randomization are excluded from the analysis under the assumption that their eligibility would be independent of the randomization allocation
Failure to initiate assigned treatment according to protocol	"Treatment policy" approach	The IE are defined as 1)not offering same-day ART in the "ART first" arm and 2) offering ART start prior to completing TB investigation in the "TB results first" arm. This IE is ignored and considered part of the intention to treat strategy
Failure to initiate ART	"Treatment policy" approach	This IE applies only to the "TB results first" arm and is ignored and considered part of the intention to treat strategy.
Discontinuation of ART	"Treatment policy" approach	This IE is ignored and considered part of the intention to treat strategy.
Transfer to another facility	"Treatment policy" approach	This IE is ignored and considered part of the intention to treat strategy.
Death due to non-trauma	"While alive" approach	Those with the IE prior to VL measurement are included as failures; those with the IE after their VL measurement are included with their endpoint.
Death due to trauma	"While alive" approach	If the endpoint is measured prior to the IE, will be included.
Death due to trauma	"Principal stratum" approach	If the endpoint is not measured prior to the IE, these individuals will be excluded assuming the IE is independent of treatment allocation.

Lost to follow-up	"Composite" approach	No viral load measured. Those with the IE would be considered to have failed treatment and are therefore included as part of the endpoint definition above.

[1] Intercurrent events are post-randomization events that affect either the interpretation or existence of the outcome data associated with the clinical question of interest. . [2] Intercurrent events are post-randomization events that affect either the interpretation or existence of the outcome data associated with the clinical question of interest. [3] The case where individuals had blood drawn for a viral load test, but the test was invalid or failed will be handle with imputation if numbers allow.

Table 2b. Estimand framework: primary outcome for non-inferiority comparison, resembling per protocol approach [1]

Estimand attribute	Definition	Comments
Population	Individuals aged 12 years or older, testing HIV-positive or known to be HIV-positive and not taking ART, with one or more TB symptoms according to WHO four-symptom screening (4WSS), who would not die from a trauma-related cause before having the endpoint measured.	Exclusion of individuals considered too ill to follow standard care (needing admission or referral, CNS symptoms, or a positive CrAg test), pregnant women, or those taking TB treatment were excluded as written in the protocol. Exclusion of individuals who die from trauma-related causes before having the endpoint measured.
Treatment conditions	Same day ART start ("ART first") vs. ART start once TB confirmed or refuted ("TB results first")	
Endpoint	HIV viral load measured and suppression <400 copies/mL 26 (22 – 40) weeks after enrolment and did not die from a non-trauma-related cause prior to 40 weeks.	Endpoint clarified to include those who die from a non-trauma-related cause or were LTFU without a VL measurement as "failures", i.e. did not achieve viral suppression.
Summary measure	Risk differences. We will also report odds ratios and risk ratios.	
Handling of intercurrent events (IE) [2]		
Ineligible	"Principal stratum" approach	Individuals found to be ineligible after randomization are excluded from the analysis under the assumption that their eligibility would be independent of the randomization allocation
Failure to initiate assigned treatment according to protocol	"Principal stratum" approach	The IE are defined as 1)not offering same-day ART in the "ART first" arm and 2) offering ART start prior to completing TB investigation in the "TB results first" arm. We are interested in the subpopulation of patients who would not experience this IE. To account for the assumption that these IE are not independent of treatment assignment, the estimator will be estimated using weighting methods (see section 6.2).
Failure to initiate ART	"Treatment policy" approach	This IE applies only to the "TB results first" arm and is ignored and considered part of the intention to treat strategy.
Discontinuation of ART	"Treatment policy" approach	This IE is ignored and considered part of the intention to treat strategy.
Transfer to another facility	"Treatment policy" approach	This IE is ignored and considered part of the intention to treat strategy.
Death due to non-trauma	"While alive" approach	Those with the IE prior to VL measurement are included as failures; those with the IE after their VL measurement are included with their endpoint.
Death due to trauma	"While alive" approach	If the endpoint is measured prior to the IE, will be included.

Death due to trauma	"Principal stratum" approach	If the endpoint is not measured prior to the IE, these individuals will be excluded assuming the IE is independent of treatment allocation.
Lost to follow-up[3]	"Composite" approach	No viral load measured. Those with the IE would be considered to have failed treatment and are therefore included as part of the endpoint definition above.

[1] Text which differs from Table 2a is shown in blue. [2] Intercurrent events are post-randomization events that affect either the interpretation or existence of the outcome data associated with the clinical question of interest. [3] The case where individuals had blood drawn for a viral load test, but the test was invalid or failed will be handle with imputation if numbers allow.

5. Trial population

5.1 Screening data

No specific screening data were captured, aside from those used to determine eligibility for the trial (see sections 3.1 and 5.2).

5.2 Eligibility

Screening/eligibility data will be summarized in a CONSORT flowchart, showing the total number of people screened and the reasons for screening failures as per the eligibility criteria in section 3.1. See template in section 8.

5.3 Recruitment

We will present graphically screening and enrolment over time. The CONSORT flowchart will include the numbers of participants randomized by arm. Enrolment will be presented by the country (stratification factor; see section 8).

5.4 Withdrawal/follow-up

The CONSORT flowchart will summarize each follow-up event (study visit and register reviews), by randomized arm. For participants who did not attend the study visit as expected, tracing information will be summarized.

5.5 Baseline patient characteristics

Baseline characteristics will be summarized by randomized group, using medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables. A shell table showing the variables and categories is included in section 8. Assessment will be made for baseline imbalances between the randomization arms by visual inspection by the trial steering committee before looking at outcome data. The primary analysis will be adjusted to include any covariates so identified (erring on the side of inclusivity). There will be no formal testing of baseline characteristics across randomized groups (5,6).

6. Analysis

Analyses will follow CONSORT guidelines, including extensions for non-inferiority trials (6–8). Analyses will include all follow up to the date of data freeze.

Analyses will be performed by the trial statistician. There will be no independent programming of the analyses, rather we rely on the training and experience of the team for the accuracy of the data, analyses and interpretations; and the results will be assessed as a whole for consistency.

Percentages will be reported to zero decimal places, unless <0.5% when they will be given to one decimal place.

6.1 Outcome definitions

Here we define outcomes for analysis. Table 1 provides the analysis windows for the occurrence of the outcomes.

TB diagnosis

A positive TB diagnosis is defined as any of the following:

- Positive Xpert MTB/RIF Ultra: positive (with or without resistance) or trace results
- chest x-ray judged suggestive of TB and requiring treatment by the responsible health care provider
- clinical judgment requiring treatment as indicated by the responsible health care provider
- positive urine TB Determine LAM (1+, 2+, 3+, 4+)

Prevalent TB: TB diagnosed through TB investigations completed up to a maximum of 28 days after enrolment

Incident TB: TB diagnosed as described above and not meeting the definition of prevalent TB.

Primary outcome

The study visit for primary outcome assessment was scheduled together with the routine 6 month ART refill visit. Study staff tried to ensure that a VL was measured for the assessment of the study primary endpoint. If VL was not successfully measured or a study visit did not occur, participants were traced in order to obtain the outcome assessment.

Viral suppression is defined as a HIV VL <400 copies/mL during the defined analysis window of 154-280 days (Table 1). The viral load was obtained from routine laboratory reports at study facilities, from laboratory reports of referral facility in case of transfer out, or from dried blood spot (DBS) sample for participants without documented clinic visit but found during home visit tracing.

If more than one VL is available for a participant during this window, any value meeting the definition of viral suppression will be considered and defined as the participant achieving the primary endpoint.

Secondary outcomes

Retention in care: A participant will be considered as retained in care if they have a documented ART clinic or refill visit at the study facility or a referral facility between 22 and 30 weeks after enrolment. Evidence of viral suppression up to week 40 is also considered as retention in care.

Engagement in care: A participant will be considered as engaged in care if they reported regular ART intake between 22 and 30 weeks after enrolment. This documentation of

regular ART intake can be taken from information provided by the participant during the study visit, retrieved from the week 30 register review, or from tracing information provided by the participant. Evidence of viral suppression up to week 40 is also considered as engagement in care.

Disengagement from care: A participant will be considered as disengaged from care if not engaged in care but the participant was verified to be alive after week 22 during patient tracing.

Lost to follow-up: A participant will be considered lost to follow-up if there is no documentation of a clinic visit between weeks 22 and 30 after enrollment and no information about the participant was found through tracing.

Non-traumatic mortality, SAEs, and AESIs: See below for definition. Any of these defined events occurring during the first 30 weeks after enrolment will be considered.

Incidence of TB disease: Diagnosis of TB between 28 days and 30 weeks after enrolment.

HIV viral suppression: As a sensitivity analysis of the primary outcome, we will consider three different thresholds for defining viral suppression (<20 copies/mL; <100 copies/mL; <1000 copies/mL). The VL tests must be done as for the primary endpoint between weeks 22 and 40 after enrollment.
Note that VL results measured using DBS have a detection limit of >100 copies/mL and therefore will not be included in the reporting of the threshold of <20 copies/mL or <100 copies/mL.

ART initiation: Any record of an individual starting ART within 7 and within 28 days after enrolment. This information is documented in the study database in a dedicated format the time of ART initiation if observed by the study team or retrospectively based on clinic records. The source can be the 26 week study visit, any register review, or the tracing data.

Exploratory outcomes

Clinical characteristics of participants with non-traumatic hospitalizations and deaths in PLHIV with presumptive TB (to be reported in a separate manuscript).

TB prevalence: Prevalence of active TB diagnosed at enrolment, defined as TB diagnosed clinically or microbiologically through the TB investigations completed up to a maximum of 28 days after enrolment.

Safety endpoints

Definitions of SAEs, and AESIs are provided below.

The study team will gather as much information as possible about all possible SAEs and AESIs. Information will be gathered about TB diagnoses, timing of ART initiation

(relative to TB diagnosis and treatment), clinical course (including documentation of relevant diagnostic and therapeutic activities by routine clinical staff), and alternative explanations for clinical symptoms. This information is a narrative clinical report compiled by the study physician using all available information from facility records, staff, patient and relatives and including judgment of study physician, National PI or delegate. Events possibly linked to TB-IRIS were presented to an independent expert clinical committee for adjudication about likelihood that symptoms are consistent with TB-IRIS. The adjudication committee will be blinded to arm allocation.

Surveillance for SAEs and AESIs
SAEs are solicited in three ways:

- Active inquiry at 26 (22-30) week study visit
- Register reviews and referral to study team by routine staff in case of relevant medical complaints
- Tracing with phone calls and home visits between week 31 and 40 to determine outcome for participants without a documented clinic visit between week 22 and 30

AESIs are captured through referral to study team by routine staff in case of relevant medical complaints. We will not inquire about AESIs at the 26 (22-30) weeks study visit or during the tracing because the long recall period will not allow for adequate documentation of AEs other than SAEs.

Definition of AEs

Adverse event (AE)	Any untoward medical occurrence in a trial participant, including occurrences that are not necessarily caused by or related to that trial procedures.
Adverse event of special interest (AESI)	AE consistent with TB IRIS (see section 7.1.3 for definition) according to judgment of independent clinical expert committee
Serious adverse event (SAE)	Any AE that: o Results in death o Is life-threatening o Requires hospitalization or prolongation of existing hospitalization o Hospitalizations due to uncomplicated delivery are not considered as SAE o Results in persistent or significant disability or incapacity o Consists of a congenital anomaly or birth defect

Definitions of causality for SAEs are as follows

Unrelated	There is no evidence of any causal relationship
Unlikely related	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial procedures). There is another reasonable explanation for the event (for example, the patient's clinical condition or other concomitant treatment).
Possibly related	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial procedures). However, the influence of other factors may have contributed to the event (for example, the patient's clinical condition).

Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Definition of TB-IRIS

We will use the Meintjes et. al. [9] definition of paradoxical and unmasking TB-IRIS.

Paradoxical TB IRIS
(A) Antecedent requirements Both of the two following requirements must be met: ● Diagnosis of tuberculosis: the tuberculosis diagnosis was made before starting ART and this should fulfill WHO criteria for diagnosis of smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extra-pulmonary tuberculosis ● Initial response to tuberculosis treatment: the patient's condition should have stabilised or improved on appropriate tuberculosis treatment before ART initiation—e.g., cessation of night sweats, fevers, cough, and weight loss. (Note: this does not apply to patients starting ART within 2 weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported) (B) Clinical criteria The onset of tuberculosis-associated IRIS manifestations should be within 3 months of ART initiation, re-initiation, or regimen change because of treatment failure. Of the following, at least one major criterion or two minor clinical criteria are required: Major criteria ● New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement—e.g., tuberculous arthritis ● New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI) ● New or worsening CNS tuberculosis (meningitis or focal neurological deficit—e.g., caused by tuberculoma) ● New or worsening serositis (pleural effusion, ascites, or pericardial effusion) Minor criteria ● New or worsening constitutional symptoms such as fever, night sweats, or weight loss ● New or worsening respiratory symptoms such as cough, dyspnea, or stridor ● New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy (C) Alternative explanations for clinical deterioration must be excluded if possible ● Failure of tuberculosis treatment because of tuberculosis drug resistance ● Poor adherence to tuberculosis treatment ● Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed) ● Drug toxicity or reaction
Unmasking tuberculosis-associated IRIS
Patient is not receiving treatment for tuberculosis when ART is initiated and then presents with active tuberculosis within 3 months of starting ART AND one of the following criteria must be met: ● Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation. Examples include tuberculosis lymphadenitis or tuberculosis abscesses with prominent acute inflammatory features, presentation with pulmonary tuberculosis that is complicated by respiratory failure due to adult respiratory distress syndrome, and those who present with a marked systemic inflammatory syndrome related to tuberculosis. ● Once established on tuberculosis treatment, a clinical course that is complicated by a paradoxical reaction

6.2 Analysis methods

Outcomes will be summarized using means and standard errors for continuous variables and numbers and percentages for categorical variables, by randomized arm.

Primary outcome analysis

The primary analysis for this study will be the comparison of viral suppression rates between the two study arms. For the primary outcome, we will summarize the numbers and percentages of participants included in the analysis, and experiencing the intercurrent events, as per Tables 2a and 2b.

The analysis will use a modified Poisson regression with a log link and robust standard errors to calculate risk differences (10,11). The model will be adjusted for country, the pre-specified randomization stratification factor. (12) Moreover, we will adjust for the most important baseline characteristics (age, gender, CD4 cell count, and ART status) if found to be unbalanced between study arms. In the case of convergence issues, we will use marginal standardization to obtain the risk differences (13).

For the non-inferiority comparison between the two arms, a CI approach will be used. A figure illustrating the confidence intervals for the risk differences and the non-inferiority margin will be presented. If the lower bound of the confidence interval for the risk difference does not include the non-inferiority margin, then the intervention will be considered non-inferior.

For the non-inferiority comparison in the per-protocol analysis, we will use weighting techniques to re-weight the population (14) to account for a potential lack of exchangeability introduced by excluding individuals where the offer of ART did not follow the intervention strategy.

In addition to the absolute effect measure of risk differences, we will report the relative effect of the intervention as well with odds ratios and risk ratios as recommended by the CONSORTs statement (6).

As per section 3.4, if the intervention is found to be non-inferior to the control arm in both the ITT and per-protocol population, then we will assess for superiority under the superiority comparison approach (Table 2a) by assessing whether the 95% CI for the risk difference excludes 0.

We will conduct a complete case analysis in which only individuals with a valid VL measurement in the endpoint window of 22 to 30 weeks is included.

We will summarize what proportion of the primary outcome information came from tracing activities.

We will conduct a planned subgroup analysis by country. Effect estimates of the primary outcome will be presented descriptively by subgroup. Potential effect modification of the primary outcome by ART status will be assessed by including interaction term between arm and the corresponding variable in the model. If the interaction term is found to be

significant (p<0.1), effect estimates will be summarized descriptively by subgroup. The study is not powered for these pre-planned subgroup analyses so all results will be considered exploratory.

Given that VLs were done through the routine health system, in Malawi, some DBS tests were done on platforms with a limit of quantification at 839 copies/mL (Abbott m2000/real time) or 883 copies/mL (Panther Hologic). After conferring with experts, we have concluded to consider these tests as suppressed at the limit of 400 copies/mL for the primary analysis if the PCR target was not detected (as opposed to target detection but not quantifiable). As a sensitivity analysis of the primary outcome, we will consider these as not suppressed.

Secondary outcomes analysis

All secondary binary outcomes will be estimated as with the primary outcome and summarized with risk differences, risk ratios and 95% confidence intervals.

The secondary outcome of HIV viral suppression at different thresholds will be analyzed similar to the primary outcome - as a non-inferiority comparison followed by superiority if non-inferiority is established but no sensitivity analyses or effect modification will be done.

The secondary endpoints of retention in care, engagement in care, disengagement from care, lost to follow-up, and ART initiation within 7 or 28 days after enrollment will be assessed for superiority in the ITT population.

Non-traumatic mortality, hospitalizations, SAEs, AESIs and incidence of TB will be summarized descriptively as events are expected to be rare.

6.3 Missing data

Missing baseline and outcome data will be summarized by study arm. Where applicable, percentages will be of non-missing values.

In the case of missing VL for the primary endpoint, when no information is available, the participant is considered to have failed (see Table 2a and 2b). However, in the case where a VL result was not available, but information about ART refills is available, we will consider using multiple imputation in a sensitivity analysis if the numbers of these cases is sufficient to warrant the additional complexity.

6.4 Additional analyses

Analyses for sub-studies will be described elsewhere.

6.5 Harms

Safety data are included as secondary endpoints (see section 6.2).

We will report by randomized arm on the number of pregnancies and safety outcomes.

6.6 Statistical software

Analyses will be conducted in Stata version 18 (15).

7. References

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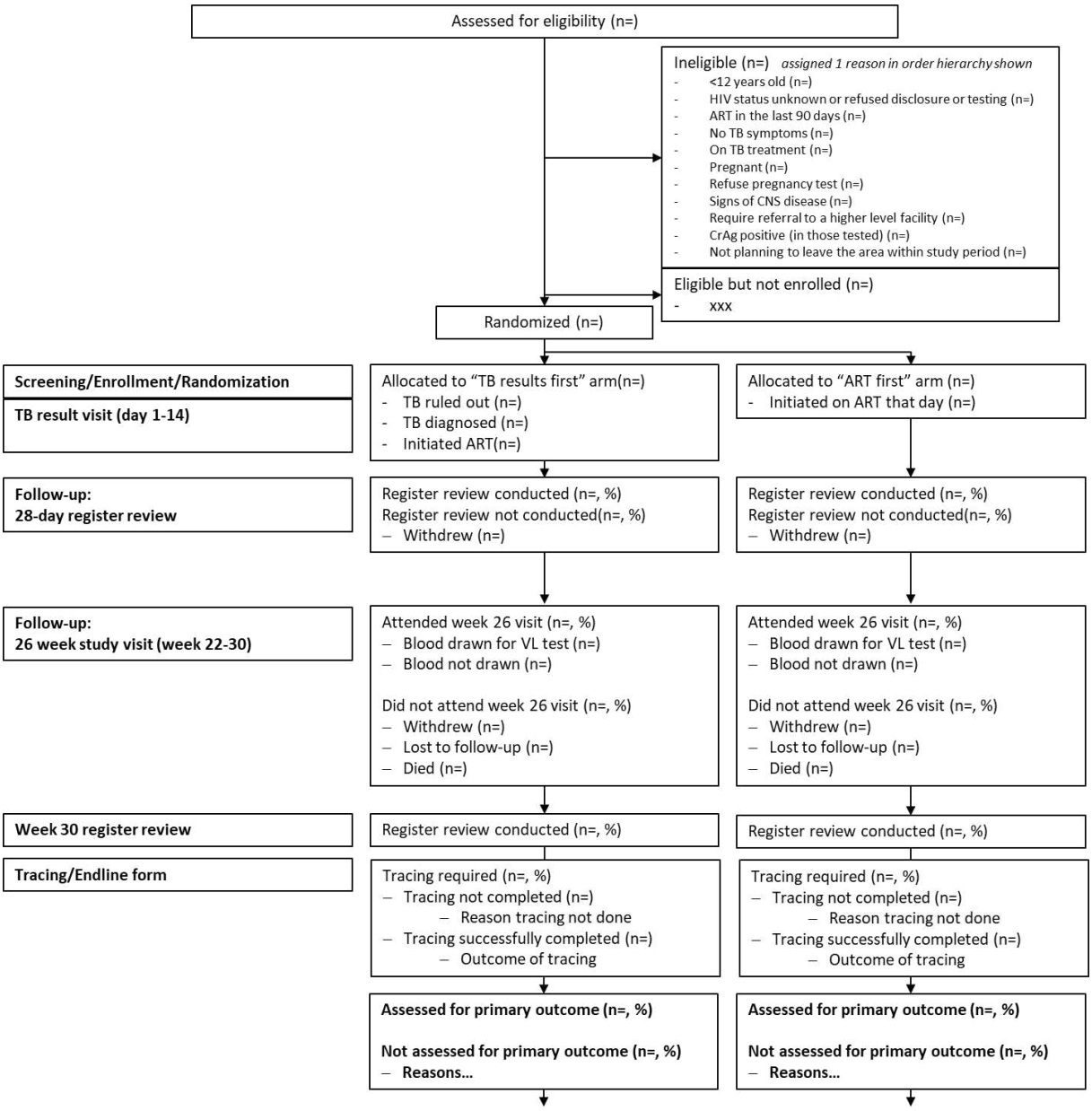
8. Shell tables and figures

Presented below are the shell tables and figures for the participant flow and baseline characteristics, to illustrate the variables included. Further tables will be included in the report to present the analyses described above, including outcomes and safety data.

8.1 Flowchart.



8.2 Baseline characteristics by randomized arm.

	TB first	ART first	Total
Number randomized			
Country			
Malawi			
Lesotho			
ART status			
Naïve			
Previously treated			
Demographics and socio-economics			
Sex, female			
Age, years			
Marital status			
Occupation			
Highest level of education completed			
Literate			
Mode of travel to the clinic			
Time to reach clinic (min)			
Cost to reach clinic			
Malawi (Malawi Kwacha)			
Lesotho (Loti/Rand)			
Wealth steps			
TB symptoms			
Cough			
Night sweats			
Losing weight			
Fever			
Health status			
Self-rated health status			
Karnofsky score			
Time since HIV diagnosis			
WHO stage			
CD4 cell count			
Vitals			
Weight, kg			
BMI			
Respiratory rate			
Heart rate			
Temperature			
Oxygen saturation			

Results are number (column % of those with non-missing data) for categorical variables and median (IQR) [range] for continuous variables.