

Clinical Study Protocol SaDAPT Trial

“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”

SaDAPT Trial

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1 GENERAL INFORMATION

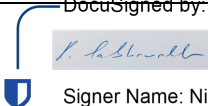
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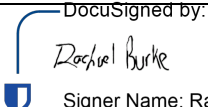
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IV. Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALHIV	Adolescents living with HIV
ART	Antiretroviral therapy
CNS	Central nervous system
COU	Clinical Operations Unit
CPT	Cotrimoxazole preventive therapy
CrAg	Cryptococcal antigen
CRF	Case report form
CRSU	Clinical Research Support Unit
DBS	Dried blood spot
DHMT	District Health Management Team
GCP	Good Clinical Practice
ICF	Informed consent form
HIV	Human immunodeficiency virus
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRIS	Immune reconstitution inflammatory syndrome
ITT	Intention to treat (analysis population)
KUHES	Kamuzu University of Health Sciences
PLHIV	People living with HIV
POC	Point-of-care
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

V. Synopsis

Sponsor-Investigator	Prof. Dr. Niklaus Labhardt, MD, DTM&H, MIH Swiss Tropical and Public Health Institute & University Hospital Basel
Study Title:	Same-day versus rapid ART initiation in HIV-positive individuals presenting with symptoms of tuberculosis: an open-label, randomized, controlled clinical trial in Lesotho and Blantyre district, Malawi
Short Title / Study ID:	SaDAPT Trial (“Same-Day ART initiation in Presumptive TB”)
Protocol Version and Date:	Version 1.2, 29.04.2022
Trial registration:	Registration is planned on clinicaltrials.gov as soon as this version of the protocol has been approved by the Independent Ethics Committees (IECs)
Study category and Rationale	Risk category A. The SaDAPT trial entails the comparison of two different algorithms for the timing of ART initiation in people living with HIV (PLHIV) presenting with symptoms of a possible tuberculosis (TB) infection but no signs of central nervous system (CNS) disease. Both approaches are in line with current national or international guidelines.
Clinical Phase:	Therapeutic use trial. The trial uses treatments and drug-doses as per international and national guidelines. All treatment components will be applied at standard dosage and no new substances or alternative indications will be tested.
Background and Rationale	<p>HIV remains a major cause of morbidity and premature death in many sub-Saharan African countries including Lesotho and Malawi. Globally, 680’000 lives were lost in 2020 in association with HIV despite the availability of effective and low-cost antiretroviral therapy (ART).¹ 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.² WHO recommends a four-symptom screening (W4SS) approach including cough, fever, night sweat and weight loss for clinical routine TB-screening among PLHIV.³⁻⁶ PLHIV presenting with at least one of the four symptoms are defined as having presumptive TB. The prevalence of presumptive TB among PLHIV not taking ART has been estimated at 71% in a systematic review.⁴</p> <p>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.⁷ PLHIV with opportunistic infections may benefit particularly from rapid ART initiation and the subsequent suppression of HIV replication and reconstitution of CD4-cell mediated immunity. At the same time, they are at risk of developing immune reconstitution inflammatory syndrome (IRIS) after initiation of ART.⁸⁻¹⁰ The risk for development of IRIS increases with earlier initiation of ART.^{8,10-13} Until the release of a guideline update in 2021,^{3,14} 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.¹⁵ 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. However, a systematic review on the effect of SDI for PLHIV with presumptive TB but no signs of CNS disease, that was conducted to inform this guideline update came to the conclusion that “there is insufficient evidence about whether presence of TB symptoms should lead to ART start being deferred or not”.¹⁶ Accordingly, 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.¹⁴</p>

Overall objective:	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 pragmatic randomized trial reflecting routine primary and secondary care setting in southern Africa.
Hypothesis	For PLHIV with presumptive TB, but no signs of CNS disease, same day ART (“ART first”) is non-inferior to rapid ART (“TB results first”) for being retained in care with suppressed HIV viral load (VL) 26 weeks after enrolment.
Endpoints:	<p>Primary endpoint</p> <ul style="list-style-type: none"> - HIV viral suppression (VL <400 copies/mL) 26 (range 22 – 40) weeks after enrolment <p>Secondary and safety endpoints</p> <ul style="list-style-type: none"> - Retention in care 26 (22 – 30) weeks after enrolment - Engagement in care 26 (22 – 30) weeks after enrolment - Disengagement from care 26 (22 – 30) weeks after enrolment - Lost to follow-up 26 (22 – 30) weeks after enrolment - Non-traumatic mortality, SAEs, and AESIs (see section 7.1 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 - 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
Study design:	Prospective, parallel, open-label, 1:1 individually randomized, non-inferiority trial
Inclusion / Exclusion criteria:	<p>Inclusion criteria</p> <ul style="list-style-type: none"> - 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 W4SS⁴ - Planning to continue care at the study facility for at least 30 weeks - Willing and able to consent (age 18 years or older) or assent with guardian consent (age 12 to 17 years) <p>Exclusion criteria</p> <ul style="list-style-type: none"> - Medical condition requiring admission or referral to a higher level health facility at enrolment - Symptoms or clinical signs suggestive for diseases of the CNS - Positive cryptococcal antigen test (CrAg) - Reporting to be pregnant - Taking TB treatment or TB preventive therapy (TPT)

<p>Measurements and procedures:</p>	<p>SaDAPT is a pragmatic trial attempting to reflect routine care in primary and secondary health facilities in Blantyre district and Lesotho. Study staff will not interfere in most aspects of patient management but primarily have a documentary role.</p> <p>Screening and Enrolment</p> <ul style="list-style-type: none"> - HIV status documentation - Clinical TB screening using the W4SS⁴ - Clinical screening for signs of CNS disease - CrAg test if CD4 cell count is < 200 cells/mm³ or upon clinical suspicion - Hand out two sputum bottles for spot and morning sputum samples for analysis with Xpert MTB/RIF (Ultra) <p>Randomization</p> <ul style="list-style-type: none"> - 1:1 randomization stratified by country <p>Routine ART care and SAE/AESI surveillance</p> <ul style="list-style-type: none"> - (Self-) referral of participants to the study facility in case of medical complaints during the whole follow-up period - Clinical management by routine staff with referral to study staff for assessment and documentation in case of possible SAE or AESI - Review of relevant routine clinical registers for the follow-up duration by study staff to detect possible SAEs or AESIs not yet captured in the trial data base - Report from site investigators to study physician or National PI in case of possible SAE or AESI for further assessment and documentation by physician if required - Reporting of SAEs to Sponsor-Investigator and ethics committee - Reporting of possible AESIs to independent clinical expert committee for classification <p>Study visit, week 26 (22-30)</p> <ul style="list-style-type: none"> - Study visit scheduled together with routine 6-month ART refill visit - Routine ART care including VL measurement by routine clinical staff - Study assessment including assessment of ART and TB status, and inquiry about SAEs since enrollment <p>Register review, week 30</p> <ul style="list-style-type: none"> - Ensure complete documentation of relevant routine register data since enrolment - Identify participants without a documented VL between week 22 and 30 <p>Tracing for outcome assessment, week 31-40</p> <ul style="list-style-type: none"> - Participants without a documented VL between week 22 and 30 will be traced via phone calls and home visits after week 30 to ascertain their outcome
<p>Study Intervention:</p>	<p>“ART first” arm:</p> <ul style="list-style-type: none"> - ART initiation on the day of enrolment independent of TB investigations <p>“TB results first” arm:</p> <ul style="list-style-type: none"> - ART initiation only after active TB has been refuted or confirmed
<p>Number of Participants with Rationale:</p>	<p>Based on the assumptions of non-inferiority of the primary outcome between the two arms, proportions of viral suppression at 26 weeks of 75% in both arms and selection of a non-inferiority margin of 10%, a power of 80%, and a one-sided alpha level of 0.025, a sample size of 590 participants will be required.</p>
<p>Study Duration:</p>	<p>First participant in: June 2022. Expected recruitment period to reach sample size: 12 months. Follow-up duration: maximum 40 weeks. Last participant out: March 2024.</p>
<p>Study Centre(s):</p>	<p>Seven primary or secondary health care facilities in Lesotho and four primary health care facilities in Blantyre district, Malawi.</p>

Statistical Considerations:	We will perform a non-inferiority comparison between the arms on the primary outcome of viral suppression at 26 weeks. Under the assumptions of the sample size calculation, the proportion of viral suppression in the “TB results first” arm is expected to be 75% and the non-inferiority margin is set at 10%. For analysis, we will use a confidence interval approach. We will do the comparison using both a per-protocol (PP) and a modified intent-to-treat (mITT) population. If the lower bound of the 95% confidence interval for the risk difference excludes -10% in both the PP and mITT population, then the intervention will be considered non-inferior. If the “ART first” arm is found to be non-inferior to the “TB results first” arm, then we will assess for superiority using the mITT set.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

2 BACKGROUND INFORMATION

2.1 The HIV-TB syndemic

Global efforts have led to a substantial decrease in HIV transmission and mortality over the past decades. Nevertheless, HIV remains a major cause of morbidity and premature death in many sub-Saharan African countries including Lesotho and Malawi, the hosting countries of this trial. 680'000 lives were lost in 2020 in association with an HIV infection, 460'000 of them in sub-Saharan Africa, despite the availability of effective and low-cost antiretroviral therapy (ART).¹⁷

The most important opportunistic infection associated with HIV is tuberculosis (TB). TB is the deadliest infectious disease globally with an estimated 1.3 million deaths among HIV-negative people and an additional 214'000 among people living with HIV (PLHIV) making it the most important cause of death in PLHIV. In low-income settings, where prevalence of HIV/TB-coinfection is highest, TB has a particularly high burden among PLHIV. Africa bears approximately one third of all deaths caused by HIV-associated TB; of the 214'000 TB deaths among PLHIV 170'000 occur in Africa.²

Globally, Lesotho and Malawi, the hosting countries of this study, are among the countries with the highest adult HIV prevalence (21.1% and 8.1% respectively)¹⁷ and TB incidence (650 and 140 per 100'000 patient-years)² leading to a particularly active syndemic of the two diseases: About half of people diagnosed with active TB are HIV-positive² in the two countries and TB causes about a third of HIV-related deaths in Malawi and more than half of HIV-related deaths in Lesotho.^{2,17}

2.2 Same-day ART initiation

An important element to improve access to ART is the implementation of rapid, if possible same-day initiation (SDI) of ART in persons found HIV positive. Rapid or same-day ART initiation improves retention in care, viral suppression and survival compared to a delayed start of ART for people with advanced HIV disease.¹⁸⁻²² In addition to improving individual health outcomes, SDI also reduces the risk of sexual transmission of HIV.²³ The World Health Organization (WHO) as well as guidelines in the US, Europe and southern Africa including Lesotho and Malawi thus recommend rapid, possibly same-day, ART initiation for patients without contraindications, who are ready and willing to start ART immediately.^{3,24-29}

Individuals with advanced HIV disease or opportunistic infections may benefit particularly from rapid ART initiation and the subsequent suppression of HIV replication and reconstitution of CD4 cell mediated immunity. At the same time, patients with advanced HIV disease or opportunistic infections, especially TB, are at increased risk of developing immune reconstitution inflammatory syndrome (IRIS) after initiation of ART.⁸⁻¹⁰ IRIS is an acute inflammatory condition often presenting with worsening or new onset of symptoms of underlying opportunistic infections, caused by an exaggerated inflammatory response after restoration of immunity through ART. The risk for development of IRIS increases with lower levels of CD4 cells at baseline, the presence of opportunistic infections, especially TB, and with earlier initiation of ART.^{8,10-13} IRIS is most deleterious in cases of central nervous system (CNS) involvement in the form of TB or cryptococcal meningitis. Therefore, rapid initiation of ART does not improve overall mortality in patients with CNS infections, but increases incidence of severe adverse events.³⁰⁻³² For manifestations of opportunistic infections such as TB outside the CNS, IRIS is less severe often resolving without medical care and optimal timing for initiation of ART remains unclear.^{30,33-35}

2.3 ART initiation in PLHIV with presumptive TB

WHO recommends a four-symptom screening approach including cough, fever, night sweat and weight loss for clinical routine TB-screening among PLHIV.³⁻⁶ PLHIV presenting with at least one of the four symptoms are defined as having presumptive TB, and should subsequently undergo microbiological TB investigations to refute or confirm the diagnosis of active TB. Routine TB investigations typically consist of providing the patient two or three sputum bottles with the instruction to return with filled bottles the next day. If the patient returns with the sputum bottles, the samples are sent for analysis using nucleic acid amplification tests (Xpert MTB/RIF (Ultra)). The prevalence of presumptive TB among PLHIV not

taking ART has been estimated at 71% in a systematic review with considerable variation between studies.⁴ Studies in Kenya and South Africa have shown that the subsequent bacteriological work-up confirmed the presence of active TB in only 5%-19% of presumptive TB cases.³⁶⁻³⁸

Until the release of a guideline update in 2021,^{3,14} WHO had recommended to delay initiation of ART in case of presumptive TB until TB has been investigated and TB treatment initiated if found TB-positive in order to reduce the risk of IRIS.¹⁵ This recommendation to defer ART for everyone with presumptive TB impairs access to same-day ART initiation for a large share of PLHIV. Whereas from a medical perspective delaying ART by a few days until a TB workup has been completed is reasonable, it may cause harm in resource-limited settings where delays between HIV diagnosis and ART initiation are associated with attrition from care, pre-treatment mortality and substantial out-of-pocket costs for patients, especially in remote areas where walking distances or transport costs to clinics are high.³⁹⁻⁴¹ In these settings, offering same-day ART to PLHIV with presumptive TB while TB work-up is done in parallel may be a valuable strategy to engage and retain more patients in care and thus improve overall clinical outcomes. The 2021 WHO guidelines update contains for the first time a “clinical consideration” to start ART in PLHIV with presumptive TB but no signs of CNS disease while rapidly investigating for TB, thus allowing SDI for this subgroup of PLHIV. This is representing an important paradigm shift with the potential to reduce the barrier to rapid initiation of ART for a large proportion of PLHIV. However, a systematic review on the effect of SDI for PLHIV with presumptive TB but no signs of CNS disease, that was conducted to inform this guideline update came to the conclusion that “there is insufficient evidence about whether presence of TB symptoms should lead to ART start being deferred or not”.¹⁶ Accordingly, the new 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, AEs and IRIS.³

In this randomized controlled trial (RCT) we will compare two different, guideline-approved algorithms for ART initiation in PLHIV with presumptive TB. In one arm, the updated WHO approach with SDI for all PLHIV with presumptive TB independent of TB diagnostic work-up will be applied (“ART first”). In the other arm, the algorithm recommended by many national guidelines and previous WHO guidelines with deferral of ART initiation until TB is excluded or confirmed and TB treatment initiated will be applied (“TB results first”). The direct comparison of the two approaches in a pragmatic, two-country RCT conducted in a representative high-prevalence setting will provide important evidence on the open question of optimal timing of ART initiation in the large subgroup of PLHIV with presumptive TB.

3 OBJECTIVES AND PURPOSE

3.1 Objectives

The overall objective of the SaDAPT trial is to compare two approaches for the timing of ART initiation in PLHIV with presumptive TB, but no signs of CNS disease in a pragmatic, randomized, therapeutic use trial reflecting a routine primary and secondary care setting in southern Africa. Both timing approaches (“ART first” and “TB results first”) are compatible with current national or international guidelines.

3.1.1 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

3.1.2 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:
 - o retention in care
 - o disengagement from care
 - o unsuppressed VL
 - o safety outcomes (SAEs, and AESIs)
 - o TB incidence
 - o proportion of PLHIV with rapid ART initiation (within 7 and within 28 days)

3.1.3 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

3.2 Scientific justification and rationale of study population

SaDAPT is a pragmatic trial, conducted in a population representative of those who would receive the interventions in real-life. The setting is the “public health approach” ART program in high HIV prevalence, low-income countries.

We will recruit adults (age 18 years and older) and adolescents (age 12 to 17 years). Adolescents living with HIV (ALHIV) will be included, because they are an important group starting ART, with particularly poor outcomes compared to adults.⁴² Information about the optimal timing of ART initiation for ALHIV is important so that specific public health approaches for ART can be made based on evidence rather than extrapolation from adults.

We will not recruit children (age 11 years or younger) as HIV treatment in children and presentation and diagnosis of childhood TB is substantially different to adult and adolescent HIV and TB. Women who are known to be pregnant (based on self-report) will be excluded because delay of ART initiation in pregnancy might lead to adverse effects on the foetus.³ Individuals who have CNS symptoms will be excluded because same day ART in the presence of CNS opportunistic infections is known to be harmful due to serious IRIS disease.^{31,43}

We will not recruit people without capacity to consent, people who are unwell so that they require admission or transfer to a higher level of healthcare at enrolment, or adolescents who present without a guardian.

Measures in place to ensure wellbeing and appropriate consent from all participants, including vulnerable participants are outlined in section 11.3.

4 STUDY DESIGN

SaDAPT is a prospective, parallel, open-label, 1:1 individually randomized, non-inferiority trial.

4.1 Endpoints

4.1.1 Primary endpoint

- 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)

4.1.2 Secondary and safety endpoints

- 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

4.1.3 Exploratory endpoints

- 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.

4.2 Measures to minimize bias

4.2.1 Randomisation

Participants will be randomly allocated to trial arms, and allocation will be made at the time of enrolment.

We will use block randomization with varying block sizes, stratified by country (Malawi and Lesotho). The randomization lists will be generated electronically by a statistician not involved in the trial, and uploaded to the study database.

4.2.2 Blinding

It is not feasible to blind participants and site investigators to arm allocation. However, we do not believe this will influence our aim of conducting a pragmatic trial evaluating the strategies of “ART first” versus “TB results first”.

For endpoint assessment, laboratory staff processing viral load samples will be blinded to arm allocation. Endpoints of death or loss to follow-up will be ascertained by site investigators and therefore not

blinded. For the endpoint assessment of AESI incidence, an expert panel will review clinical data, blinded to arm allocation.

4.3 Study duration and duration of participant's participation

Enrolment of first participants is scheduled for June 2022. A recruitment time of about 12 months is expected to be required to reach the calculated sample size. Final study visit is scheduled 26 (range 22 – 30) weeks after enrolment. If after this period the endpoint could not be assessed because the participant did not return to the study facility, a tracing period between week 31 and 40 is scheduled to ascertain the outcome of these participants.

4.4 Early termination of the study

4.4.1 Discontinuation on individual level

Participants can withdraw their consent to participation at any time. Anonymized data until the withdrawal will remain in the database. All personal data will be deleted in case of withdrawal of consent.

Individual participants will only be removed from the study if information later comes to light that they were not eligible for the study at the time of recruitment (i.e. someone subsequently discovered to have already been taking ART at the time of study enrolment). Female participants falling pregnant during the follow-up period of the study will not be discontinued.

4.4.2 Discontinuation of entire study

As this trial uses licensed drugs and licensed doses for licensed indications in two different timing approaches, the risk of significant harm is low. Therefore, we do not plan to have a formal interim analysis. However, there will be a data safety monitoring board (DSMB) session after 9 months of recruitment to review blinded data regarding safety parameters (see section 0).

Additionally, the Sponsor-Investigator in consultation with Co-Investigators may choose to either discontinue the study, or convene an ad hoc meeting of the DSMB to review unblinded data and to assist decision making about trial continuation at any time. Similarly, if the DSMB has concerns after seeing blinded data, they may ask for a meeting to review unblinded data.

The reasons to discontinue the study, or convene the DSMB to review data and consider discontinuing the study including the following;

- Slow or insufficient recruitment
- Alteration in accepted clinical practice that make the continuation of the study unwise.
- Insufficient support/ willingness of routine staff at the study sites to adhere to the study procedures
- Any other ethical concerns

The Sponsor-Investigator may terminate either the entire study or a single study site.

The Sponsor-Investigator would provide the National PI and the study site(s) concerned written notice submitted at a reasonable time in advance of the intended discontinuation. If the Sponsor-Investigator chooses to terminate or pause the study for safety reasons, he will immediately notify all concerned investigators and subsequently provide written instructions for study termination. The National PIs may also terminate or pause the study at one or several of their sites for a reasonable cause, after providing written notice to the Sponsor-Investigator a reasonable time in advance of the intended discontinuation. In case of discontinuation due to safety concerns, no advance notice is required.

5 SELECTION OF THE STUDY PARTICIPANTS

5.1 Study setting

The study will be conducted at primary and secondary level clinics in Lesotho and Blantyre district, Malawi.

5.1.1 Lesotho

Lesotho is a small, landlocked country surrounded by South Africa. It has the second highest HIV prevalence globally with an adult prevalence of 21.1%.¹⁷ For the trial we plan to recruit participants at seven health facilities in the districts of Butha-Buthe (Butha-Buthe Hospital and Seboche Hospital), Mokhotlong (Mapholaneng Health Centre, Mokhotlong Hospital), Leribe (Motebang Hospital), Berea (Teyateyaneng Hospital) and Maseru (Senkatana Hospital). Apart from Teyateyaneng Hospital, we have already collaborated with all sites in previous or ongoing trials.⁴⁴ Each of these clinics serves between 1000 and 8000 patients taking ART and (re)engages between 100 and 300 patients on ART per year. In these clinics, direct patient care is usually provided by nurses.

5.1.2 Blantyre district, Malawi

In Malawi, we will recruit participants from four trial sites in the Blantyre district. The HIV and TB prevalence in Blantyre is estimated at 16.7%⁴⁵ and 0.9%⁴⁶, respectively. The four sites, Bangwe Health Centre, Limbe Health Centre, Zingwangwa Health Centre and Ndirande Health Centre are staffed by mixture of clinical officers (clinicians with three years training), nurses, senior health surveillance assistants and medical assistants (lower cadres of staff). All sites provide HIV testing and care, and TB diagnosis and care services. Bangwe Health Centre in the East of Blantyre, was the site of the PROSPECT trial.⁴⁷ We have an existing research office co-located at Bangwe Health Centre and many experienced trial research staff familiar with this location. There are 360 to 480 people who newly initiate ART each year at Bangwe. Ndirande clinic is in the North of Blantyre and was the site of the ACT-TB trial from 2018 to 2020⁴⁸, which was a trial of antibiotics as a test-of-treatment for people with TB symptoms whilst awaiting TB tests. They have 300 to 360 people newly initiating ART each year, excluding pregnant women. Limbe clinic is East of Blantyre and was also a site for ACT3 TB trial.⁴⁸ There are 420 to 480 people who newly initiate ART each year at Limbe, excluding pregnant women.

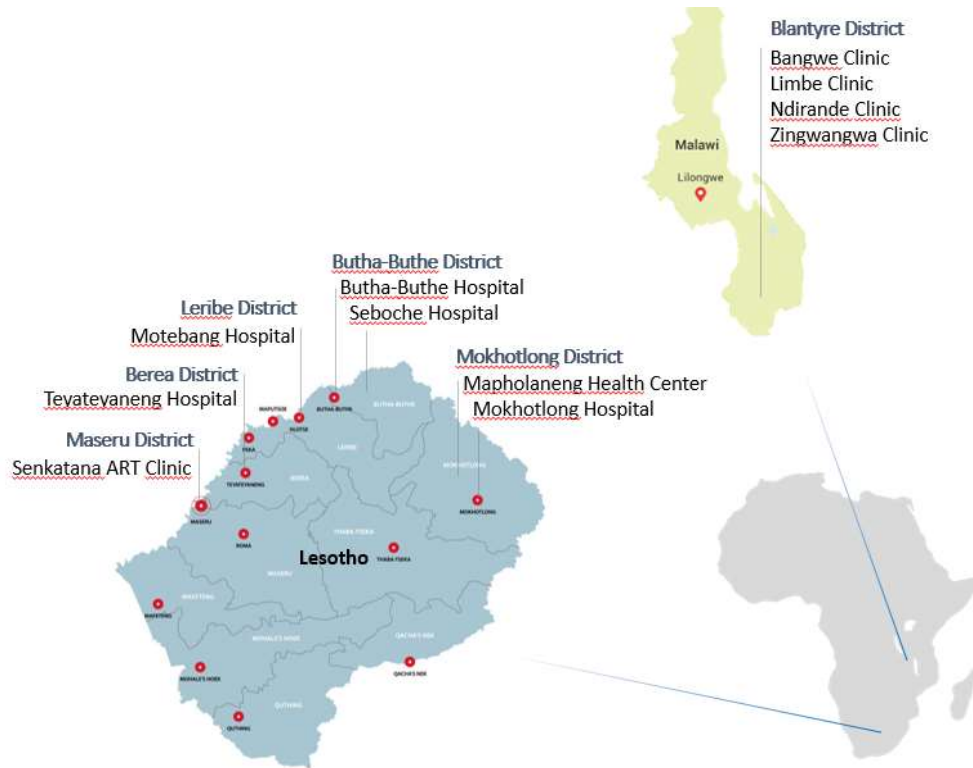


Figure 1 Map of study sites in Lesotho and Blantyre district, Malawi

5.2 Recruitment

Participants will be recruited among individuals presenting at one of the study clinics. Routine staff of all study clinics will be 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 will then screen potentially eligible individuals based on the below-mentioned inclusion and exclusion criteria and approach them for consent. See section 6.1 for screening procedures and section 11.3 for information about consent process.

5.3 Inclusion and exclusion criteria

5.3.1 Inclusion criteria

- 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 4WSS⁴
- 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)

5.3.2 Exclusion criteria

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

6 STUDY PROCEDURES

We are conducting a pragmatic study attempting to reflect routine care with as little influence by the study activities as possible. To facilitate understanding of the flow of events, we are presenting procedures conducted by routine clinic staff and study staff jointly with indication of responsible cadre in the paragraph header. For the content and timing of procedures conducted under the responsibility of routine clinical staff, we are describing what is expected to happen according to local guidelines and practices. However, deviations by routine clinical staff from what is described in the sections below are not considered study protocol deviations and are not affecting the participants' retention in the trial.

6.1 Screening and informed consent (study staff)

See section 11.3 for information about informed consent process, including for vulnerable participants. Potential participants will be asked for verbal consent to study screening. The screening process including oral screening consent will be documented in the electronic trial database. If screening consent is provided, a site investigator will screen for inclusion and exclusion criteria as outlined in section 5.3 including clinical screening for potential CNS disease. Written consent for study participation will be obtained if all inclusion criteria and no exclusion criteria are met. The study will be explained to individuals identified as potential participants (and their guardian if age 12-17 years) and an information leaflet will be handed out. Consideration will be given to ensuring privacy and confidentiality.

6.2 Randomization (study staff)

Stratified randomization will be performed as outlined in section 4.2.1. Allocation will be revealed to study staff electronically on the study tablet. Study staff will inform routine staff about arm allocation.

6.3 Baseline assessment (study staff)

Enrolment will take place in an environment as private as possible, within the constraints of the clinic setting, so that confidentiality can be assured.

On enrolment, the following procedures will be performed:

- Brief clinical history and physical examination including:
 - o HIV, ART, TB and general clinical history
 - o Sociodemographic characteristics, health status, possible comorbidities and co-mediations
 - o Measurement of height and weight with determination of BMI and vital signs
- CD4 cell count
 - o If available via routine laboratory procedures or if routine CD4 cell count is not available via point-of-care CD4 test provided by the study team
- Microbiological TB investigation
 - o Provision of one sputum bottle with instruction of on-spot sputum sample for analysis with Xpert MTB/RIF (Ultra)
 - o A second sputum bottle will be given to the participants with the instruction to collect sputum in the morning of the following day and to bring it to the clinic for analysis with Xpert MTB/RIF (Ultra)
 - o If a urine lipoarabinomannan (LAM) test or any other additional examinations are performed by the responsible routine clinic staff as part of standard of care, the results will be registered by study staff. No LAM assays will be provided by the study team.
- Collection of a DBS and two tubes of venous blood for centrifugation and storage and subsequent HIV genotyping and resistance testing

6.4 ART initiation (study staff and routine staff)

6.4.1 “TB results first” arm

The study staff will instruct routine staff that ART initiation should be deferred until results of TB work-up are available. In case TB is diagnosed on the day of enrolment (positive Xpert MTB/RIF (Ultra), clinical judgement by responsible health care provider or any other TB test (LAM) if part of routine care), TB treatment and ART may be initiated together on that day.

6.4.2 “ART first” arm

The study staff will instruct routine staff to offer same-day ART, independent of completion of TB assessment.

6.5 Further procedures on enrolment day (routine staff)

HIV and ART counselling as well as Cotrimoxazole preventive therapy (CPT) prescription will be done by routine clinic staff, according to national guidelines.^{28,29} Depending on the decision of the health care professional in charge and availability at the clinic, further investigations may be conducted, i.e. chest x-ray or urine LAM. The study team will register CPT prescription and results of any additional investigations but not intervene actively.

6.6 TB test results review, (routine staff)

The following procedures are expected to be conducted by routine care providers within one week after enrolment. The study staff will not intervene at this moment.

6.6.1 Both arms:

- Discussion of completed TB work-up (sputum Xpert MTB/RIF (Ultra) and clinical assessment)
- Diagnosis of TB disease (Xpert MTB/RIF (Ultra) positive and/or clinical judgement by responsible health care professional): start TB treatment as per national guidelines^{29,49,50}
- TB disease excluded (Xpert MTB/RIF (Ultra) negative and clinical decision that active TB is unlikely): start TB preventive treatment (TPT) as per national guidelines^{28,29}

6.6.2 “TB results first” arm:

- Initiate ART as per national guidelines^{28,29}

6.6.3 “ART first” arm:

- Continue ART

6.7 Routine follow up (routine staff) and SAE/AESI surveillance (study staff)

ART care (including TB symptom screening at each visit) as well as management of medical problems during the follow-up period will be provided by routine staff according to national guidelines^{28,29}. Participants will be instructed to return to the study facility in case of medical problems any time during the study follow-up. Visits will be documented by routine clinical staff in the specific routine clinical registers (see section 8.1). The clinical management during study follow-up will remain at the responsibility of the routine clinical staff. Routine clinical staff will be instructed to refer study participants to the study team for further assessment and trial documentation in case of a relevant medical problem, especially if suspecting a possible SAE or AESI. Routine staff will be trained prior to the start of the study to recognize conditions potentially relevant for the study, especially on the recognition of possible SAEs and AESIs. In addition to direct referral of participants by the routine clinical staff, the study team will review all relevant routine registers at the study facility searching all entries made during the follow-up period of an individual participant to screen for documentation of possible SAEs or AESIs not otherwise captured in the trial data base. Study staff may review routine registers any time during the follow-up period. The periods for which the registers have been reviewed will be documented by

the site investigators to avoid double-entries or skipping of time periods. Site investigators must analyze all entries made in the registers during the follow-up period and they must document all possible SAEs and AESIs encountered into the trial data base. Site investigators may document visits without occurrence of a possible SAE or AESI, however documentation of uncomplicated visits is not mandatory. The study staff's main responsibility during the follow-up period is the assessment and documentation of possible SAEs and AESIs. In case a participant is referred directly to the study staff, the site investigators will perform a brief medical history, a targeted physical examination and document results together with information about diagnostic investigations and prescriptions by routine staff in the trial database. For events notified to the study staff after the participant has left the study clinic or for events detected during the review of routine registers, the site investigators will capture as much information as possible about the event from clinical routine registers, inquiry of responsible routine staff and via phone calls to participants or relatives if required. If site investigators detect a possible SAE or AESI, the study physician or National PI will be informed by the site investigators. The study physician or National PI will assess the data provided by the site investigators and decide whether further assessment and documentation of the case is required. Possible further documentation may be conducted by the study physician or National PI him- or herself or may be delegated to other qualified study staff including the site investigators after reception of instructions for appropriate documentation of the case. All information captured by the study physician or National PI or her/his delegate will be saved in the electronic trial data base together with the information captured previously by the site investigators and will later be used for notification to the Sponsor-Investigator and IECs in case of SAEs or for the assessment by the clinical expert committee for classification in case of possible AESIs.

6.8 Study visit, week 26 (week 22 - 30) (routine staff and study staff)

The study visit will be scheduled together with the routine 6 month ART refill visit. Study staff will ensure that a VL gets measured for the assessment of the study endpoint. In addition to adherence counseling and ART refill by routine staff, study staff will take a targeted clinical history including inquiry about ART and TB status, current health status, medication, adherence and possible SAEs since enrollment. Collection of a DBS and two tubes of venous blood for centrifugation and storage and subsequent HIV genotyping and resistance testing.

6.9 Register review, week 30 (study staff)

Study staff may review routine registers any time during the follow-up period, however, for all participants a final review 30 weeks after enrolment is mandatory to ensure that the entire follow-up period has been covered and that all relevant routine registers data since enrolment (SAEs, possible AESIs, ART status, VL) are documented in the trial data base. In addition to ensuring complete documentation of relevant routine registry data for the entire follow-up period, site investigators will identify participants without a documented clinic visit during the study visit window (week 22 – 30) who will be traced for outcome ascertainment (see below).

6.10 Tracing for outcome assessment, weeks 31 - 40 (study staff)

Participants without a documented VL measurement at the study facility between week 22 and 30 after enrolment will be traced via phone calls and home visits if required between weeks 31 and 40 after enrolment to ascertain their outcome.

In case of documented transfer out, the referral facility will be contacted to obtain a VL laboratory report and the participants will be contacted via phone for assessment of engagement in care and possible SAEs during the follow-up period.

For participants without a documented VL between week 22 and 30 and no documented transfer out, a DBS and if possible two tubes of venous blood (may not be possible for example for household visits) for VL measurement and storage will be collected and the reasons for not having attended a clinic visit

between week 22 and 30 will be inquired together with assessment of engagement in care and possible SAEs during the follow-up period. If participants are not engaged in care anymore, the study team will re-link them by giving them an appointment at the health facility.

In case participants cannot be traced back, but relatives or friends of the participants can be contacted (contacts provided by the participants at enrolment), they will be asked about the presumed outcome of the participant. If friends or relatives report a transfer out, the reported referral facility will be contacted to obtain a VL laboratory report. If a participant has died, circumstances of death (in particular whether death was due to trauma and whether TB was diagnosed prior to death) will be recorded.

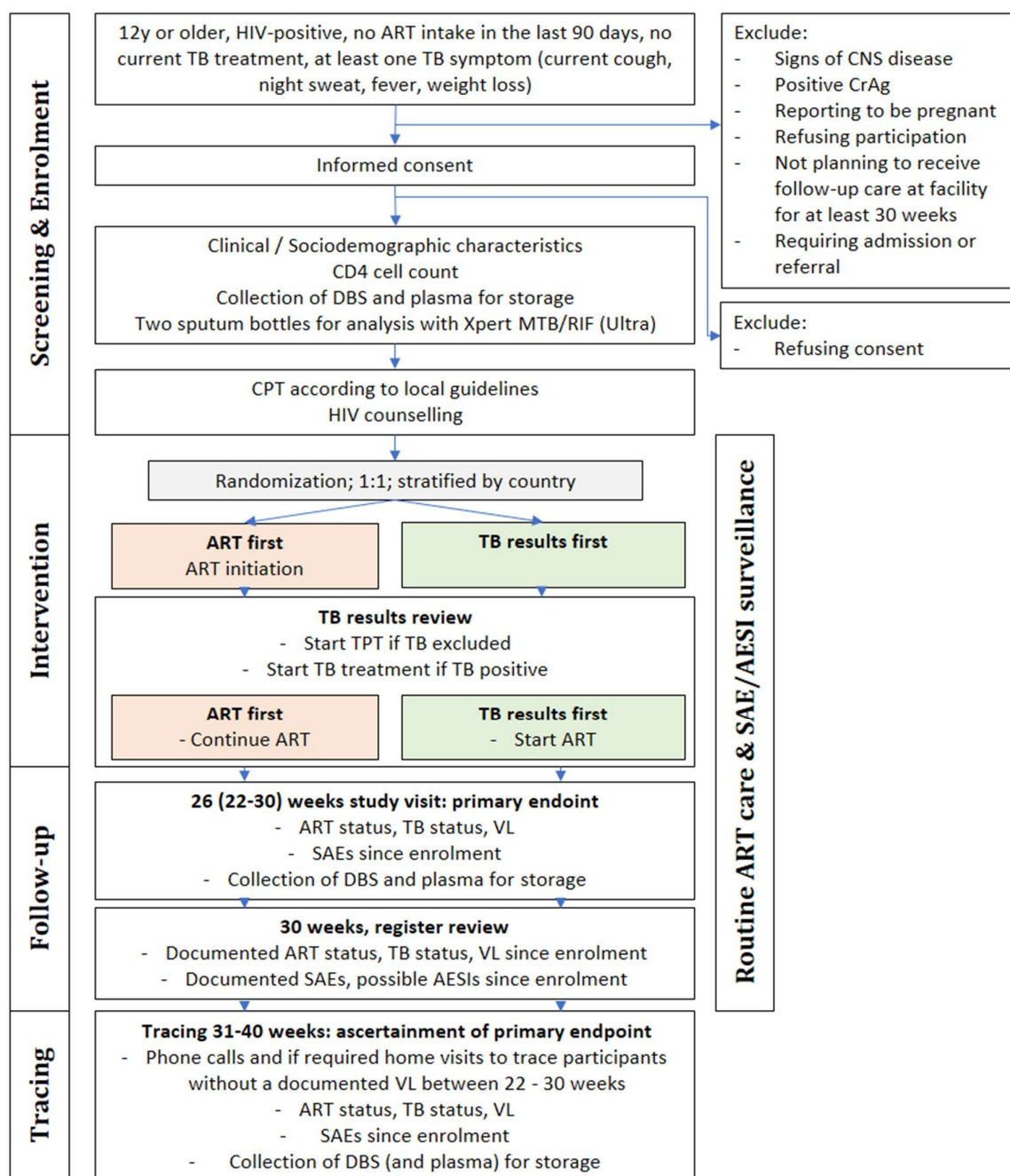


Figure 2 Flow of events SaDAPT Trial CNS: Central nervous system, CrAg: Cryptococcal antigen, DBS: Dried blood spot, CPT: Cotrimoxazole preventive therapy, TPT: TB preventive therapy, SAE: Serious adverse event, AESI: Adverse event of special interest, VL: Viral load

6.11 Schedule of events

TIMEPOINT	0 Screening enrolment	TB results	Week 26 (22-30) Study visit	30 week Register review	Weeks 31-40 Tracing ¹
Eligibility screening	X				
Arm allocation	X				
INTERVENTION ²:					
ART initiation ("ART first arm")	X				
ART initiation ("TB results first arm")		X ³			
ASSESSMENTS:					
Questionnaire (including brief medical history)	X		X		(X)
Brief physical examination	X		X		(X)
CD4 cell count	X				
CrAg test if CD4 <200 cells/ml or clinical indication	X				
Provision of TB sputum bottles ⁴	X				
DBS and plasma tube	X		X		(X) ⁷
SAE and AESI surveillance ⁵	(X)	(X)	(X)	(X)	
HIV Viral Load			X		(X)
Record review: Date of clinic visits, ART status, TB status				X	
ROUTINE CARE:					
ART counselling	X	X	X		
ART refills ⁶			X	(X)	(X)
Start TB treatment or TPT ⁶		X			
Ongoing clinical care as required	(X)	(X)	(X)	(X)	(X)
Start CPT ⁶	(X)				

¹Tracing via phone calls and home visits if no documented VL in endpoint assessment window at 22-30 weeks

² ART provision by routine services, the trial intervention is to allocate the timing of ART

³ ART start if not diagnosed with TB disease, if TB disease diagnosed ART may be delayed up to 14 days– according to national guidelines

⁴ Study staff will provide sputum bottles and instructions for TB testing to participant and routine staff to follow up results

⁵ AE surveillance; participants, family members and routine staff are asked to contact study team in case of medical complaints. Referral to study team for in case of suspected SAE or TB-IRIS

⁶ According to national guidelines

⁷ If no documented VL between week 22 – 30

7 SAFETY CONSIDERATIONS

SaDAPT is not a trial of an investigational medicinal product, all drugs used are licensed for the indications and doses used in this trial. Both arms are strategies that have been endorsed by national or international guidelines. SaDAPT is a pragmatic trial embedded within a “public health” ART system, designed to evaluate effectiveness of ART timing strategies in conditions as close to routine practice as possible.

The expected relative safety of the interventions and the desire to alter standard care as little as possible have informed our safety procedures and reporting.

7.1 Safety reporting

7.1.1 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 judgement of independent clinical expert committee
Serious adverse event (SAE)	Any AE that: <ul style="list-style-type: none">○ Results in death○ Is life-threatening○ Requires hospitalization or prolongation of existing hospitalization<ul style="list-style-type: none">○ Hospitalizations due to uncomplicated delivery are not considered as SAE○ Results in persistent or significant disability or incapacity○ Consists of a congenital anomaly or birth defect

7.1.2 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.

7.1.3 Definition of TB-IRIS

We will use the Meintjes et. al. definition of paradoxical and unmasking TB-IRIS.⁸

<p>Paradoxical TB IRIS</p> <p>(A) Antecedent requirements</p> <p>Both of the two following requirements must be met:</p> <ul style="list-style-type: none">• Diagnosis of tuberculosis: the tuberculosis diagnosis was made before starting ART and this should fulfil 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) <p>(B) Clinical criteria</p> <p>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:</p> <p>Major criteria</p> <ul style="list-style-type: none">• 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) <p>Minor criteria</p> <ul style="list-style-type: none">• 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 <p>(C) Alternative explanations for clinical deterioration must be excluded if possible</p> <ul style="list-style-type: none">• 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
<p>Unmasking tuberculosis-associated IRIS</p> <p>Patient is not receiving treatment for tuberculosis when ART is initiated and then presents with active tuberculosis within 3 months of starting ART</p> <p>AND one of the following criteria must be met:</p> <ul style="list-style-type: none">• 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

The study team will gather as much information as possible about all possible 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 (including judgement of study physician, National PI or delegate) will be 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.

7.1.4 Surveillance for SAEs and AESIs

SAEs are solicited in three ways (see section 6)

- 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 register reviews and 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.

7.1.5 Management of AEs

All participants are under the care of qualified healthcare professionals through the routine ART and TB services and study staff will not intervene in care.

7.1.6 Reporting of SAEs

Site investigators will document any SAE in dedicated CRFs and inform a study physician or the National PI about any SAE.

Study physicians or the National PIs are responsible for making an initial assessment of likely causality and reporting SAEs to the Sponsor-Investigator.

If an SAE is thought to be possibly, probably or definitely related to the study intervention, or if the study physician or National PI is unsure, this should be reported to the Sponsor-Investigator within 72 hours of becoming aware of the event. All deaths should be reported to the Sponsor-Investigator within 72 hours of being aware, regardless of causality. A follow-up report with more details of circumstances of the SAE will be made within 7 days of being aware and communicated to the Sponsor-Investigator. These reports will be reviewed by the Data Safety and Monitoring Board (DSMB).

All SAEs that are thought to be possibly, probably or definitely related to the study interventions will be reported to the ethics committees within 14 days.

7.2 Data Safety and Monitoring Board and Interim Assessment

We will recruit a DSMB with three independent expert members. A DSMB charter will outline their responsibilities in detail.

All SAEs will be reported to DSMB, along with an assessment of causality.

By default this information will be reviewed at a meeting at 9 months after first participant is recruited without unblinding of arm allocation. However if there are any safety concerns before this, the Sponsor-Investigator should ask for an earlier review by DSMB, and either the Sponsor-Investigator or any DSMB member can request a meeting to review unblinded safety and outcome data so that the DSMB can provide recommendations about trial termination or modification.

8 DESCRIPTION OF DATA MANAGEMENT

8.1 Specification of source documents

Source data includes the original records from which information related to the study is derived and may be in electronic or paper format. The source documents for this study include the completed electronic case report forms (eCRF) in the study database for results of physical examination and medical history that go beyond the detail documented in routine clinical registers, as well as ART registers, pharmacy / dispensing ledgers, TB test registers, TB diagnosis registers and routine clinic electronic medical records systems. Finally, information may be collected from computers in the diagnostic laboratory and paper-based laboratory reports.

8.2 Data management system

A comprehensive Data Management Plan will be developed prior to the start of data collection, which will outline the data management products, software and procedures for data collection, management and review. All study team members responsible for data entry and data management will be appropriately trained. The National Principal Investigators have the overall responsibility for data quality and will take reasonable measures to ensure the completeness and accuracy of the study data. Data managers and monitors will regularly review the data. Queries regarding inconsistencies, incoherencies and missing data will be raised within the electronic data capture (EDC) system. All user-specific data processing operations (creation, modification and deletion of patient records) will be recorded in a computer-generated time stamped audit trail.

Data collection will be conducted online (with offline data collection possible where internet or mobile connectivity is insufficient) via the eCRFs developed in a validated installation of the Research Electronic Data Capture (REDCap) platform⁵¹, validated by the Department of Clinical Research (DKF) at the University Hospital Basel, Switzerland. REDCap supports online and offline data capture and provides compliance with 21 CFR Part 11, FISMA, HIPAA, and GDPR. Study data related to screening, demographics, medical history, clinical examination findings, laboratory results and tracing information will be collected and entered into the eCRF by dedicated study personnel using password protected tablets. The EDC system will be hosted by the Department of Clinical Research (DKF) at the University Hospital Basel, Switzerland, and stored on a secure and encrypted server maintained by the IT-department of the University Hospital Basel. Data management will be performed by the Clinical Statistics and Data Management Unit, Swiss TPH.

8.3 Confidentiality and coding

At all times, the study data will be handled with the uttermost discretion and only be accessible by authorized personnel who require the data to fulfil their duties within the scope of the project. Each site will have a single, password-protected tablet. The eCRF will contain a master list form capturing personally identifying information such as name, date of birth and contact details for the purpose of identification by site investigators during follow-up, including tracing. Identifiable data will only be accessible by the respective site investigator for study implementation and data collection purposes and the trial data manager overseeing the electronic database, and will not be included in any exported data or metadata. Study participants will be allocated a unique participant number, which will be used to identify participants in the eCRFs and in all data exports. The investigators will respect participants' privacy according to all applicable privacy laws. Only anonymized study data will be published in scientific journals and presented at scientific meetings and conferences. All participant personal and medical information are confidential and disclosure to third parties is prohibited. Access to identifiable data for the purpose of data quality control may be granted upon request to the National Principal Investigator, the Sponsor-Investigator and other members of the study team responsible for data quality control.

8.4 Retention and destruction of study data and biological samples

At the conclusion of the study or premature termination, all study data will be locked and archived. The electronic database will be locked and a complete study dataset will be transferred to the statistician and Sponsor-Investigator through a secure channel. The eCRF and study data will be stored in the EDC software and stored by DKF on the University Hospital Basel servers for 25 years. Paper-based informed consent forms will be kept at the study sites with the site investigators being responsible for safe storage or at a later phase at a central point in each country with the National PI being responsible for safe storage for at least 10 years after termination of the study. Collected DBS and plasma samples for future HIV genotyping and resistance testing will be kept for a maximum of five years and destroyed thereafter. In Lesotho, samples will be stored in the Seboche Hospital Laboratory; in Malawi at the Kamuzu University of Health Sciences TB laboratory.

8.5 Data security, access, archiving and back up

All study data will be managed securely, in accordance with local regulations and encrypted and password protected in the EDC system, including a full audit trail. All principles of European General Data Protection Regulations will apply, unless these conflict with Malawi or Lesotho regulations, in which case the national regulations will apply.

Direct access to eCRFs and the digital data base will be permitted for purposes of monitoring, audits and inspections. Full details of data sharing and access will be outlined in a Data Sharing Agreement.

The EDC system will allow for a database freeze to avoid data from being changed by data collectors without authorization from the Data Manager. A database lock will also be enabled that will be used for final statistical analyses and prevent any further changes after final data entry and query resolution. This will be implemented according to agreed timelines.

The database design specification, study data and metadata will be archived by the trial data management on Swiss TPH servers for 25 years. For the servers on which study data will be stored, there is a defined policy in place for server set up, maintenance and security. This includes processes regarding server qualification, backups, disaster recovery and restricted server access.

Following completion of the study, anonymized individual data will be made freely available on a suitable repository concurrent with publication of initial results. Participants will be asked to consent to this at the time of enrolment.

Further details will be outlined in the Data Management Plan.

9 STATISTICS

9.1 Sample size

The sample size has been calculated with regard to the primary endpoint of the study. Secondary endpoints have not been 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 expected to be 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.

9.2 Analysis

All analyses will be done by the trial statistician using R (the R Foundation for Statistical Computing) or Stata (version 14, Stata Corporation, Austin/Texas, USA). Analysis will follow CONSORT guidelines.^{52,53} A flowchart will describe the inclusion and follow-up of participants by study arm. Baseline characteristics will be described by study arm with summary statistics such as median and interquartile range or number and percentage; no formal testing between arms will be performed. Outcomes will be described by arm using summary statistics. A detailed statistical analysis plan will be developed separately

The following analysis sets will be used in this trial:

1. Modified Intention-to-treat (mITT): anyone found to be ineligible after randomization (i.e., pregnant, had not been off ART for ≥ 90 days, etc.) will be excluded.
2. Per-protocol (PP) set: This set includes all participants who completed the study without a major protocol deviation (definitions in Statistical Analysis Plan).
3. Complete-case set: all individuals for which the endpoint data could be ascertained.

9.2.1 Primary analysis

The primary analysis for this study will be the comparison of viral suppression rates between the two study arms. Individuals who do not have documented VL 22 – 40 weeks after enrolment, died, transferred out without a documented VL, or were lost to follow-up will be considered to have a negative outcome (i.e., not achieved viral suppression). The analysis will use a logistic regression model adjusted for the pre-specified randomization stratification factors.⁵⁴ Moreover, we will adjust for the most important baseline characteristics if found to be unbalanced (gender, age, ART naive vs reinitiating ART, number and type of TB symptoms) between study arms.⁵⁵ 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. Primary analyses for the non-inferiority comparison will be performed on the mITT, per-protocol, and complete case sets.⁵⁶ If the “ART first” arm is found to be non-inferior to the “TB results first” arm in the mITT and per-protocol sets, then we will assess for superiority using the mITT set. Further details will be provided in the statistical analysis plan.

As a sensitivity analysis for the primary analysis, primary endpoint information obtained from the tracing visit will not be included.

9.2.2 Secondary, subgroup and exploratory analysis

The secondary endpoints of ART initiation within 7 or 28 days after enrollment and retention in care will be assessed for superiority. Secondary endpoints will be analyzed with logistic regression models adjusted for stratification factors and results will be presented as risk differences and 95% confidence intervals.

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

We plan to assess the potential effect modification of key factors (age groups, CD4-count, country) on the primary outcome by including interaction terms in the model. If the interaction term is found to be significant, 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.

The statistical analysis plan will provide all further details.

10 DUTIES OF THE INVESTIGATORS

10.1 Investigator's confirmation

This study will be conducted in compliance with this protocol, the International Conference on Harmonisation Good Clinical Practice E6 (R2) (ICH-GCP) and the current version of the Declaration of Helsinki.

All protocol modifications will be documented in writing. A protocol amendment can be initiated by either the Sponsor-Investigator or any investigator. The concerned investigator will provide the reasons for the proposed amendment in writing and will discuss with the Sponsor-Investigator. Any protocol amendment must be approved and signed by the Sponsor-Investigator and must be submitted to the appropriate Independent Ethics Committees (IECs) for information and approval, in accordance with local requirements. Approval by IECs must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study participants, or when the change involves only logistical or administrative aspects of the study.

10.2 Project management

The SaDAPT trial will be overseen and managed by a steering committee led by the Sponsor-Investigator Niklaus Labhardt. The steering committee will consist of representatives of the following project partners: Clinical Research Unit of the Swiss TPH, University Hospital Basel, Helse Nord Tuberculosis Initiative Malawi, Kamuzu University of Health Sciences (KUHES), SolidarMed Lesotho, Ministry of Health of Lesotho, London School of Hygiene and Tropical Medicine, Malawi Liverpool Wellcome Trust Clinical Research Programme, and the Liverpool School of Tropical Medicine.

For implementation in Lesotho, a subcontract with the Lesotho office of SolidarMed has been signed. SolidarMed is a Swiss not-for-profit organization, working in Lesotho for over 50 years (www.solidarmed.ch). Of note, SolidarMed is a long-standing implementing partner of the Sponsor-Investigator, the SwissTPH and the Ministry of Health in Lesotho. SolidarMed has the responsibility to coordinate the trial in Lesotho. For implementation of the study, SolidarMed will provide infrastructure, such as cars, office space, study personnel, and logistic and administrative support. The person responsible for the project at SolidarMed is Irene Ayakaka, technical director of SolidarMed Lesotho and National PI of this trial, who has extensive experience in project planning and implementation in Sub-Saharan Africa.

For implementation in Malawi, a subcontract with the Kamuzu University of Health Sciences (KUHES) will be signed. KUHES has the responsibility to coordinate the trial in Malawi. For implementation of the study KUHES will provide infrastructure, study personnel, and administrative support. The person responsible for the project at KUHES is Marriot Nliwasa, Research Group Leader and National PI of this trial, who has successfully led the implementation of various clinical trials on TB and HIV Malawi.

In each study country, the National PIs will support data collection and conduct data quality checks at national level. Data management at trial level will be hosted at SwissTPH under the responsibility of the trial statistician Tracy Glass who will also be responsible for statistical analyses of trial.

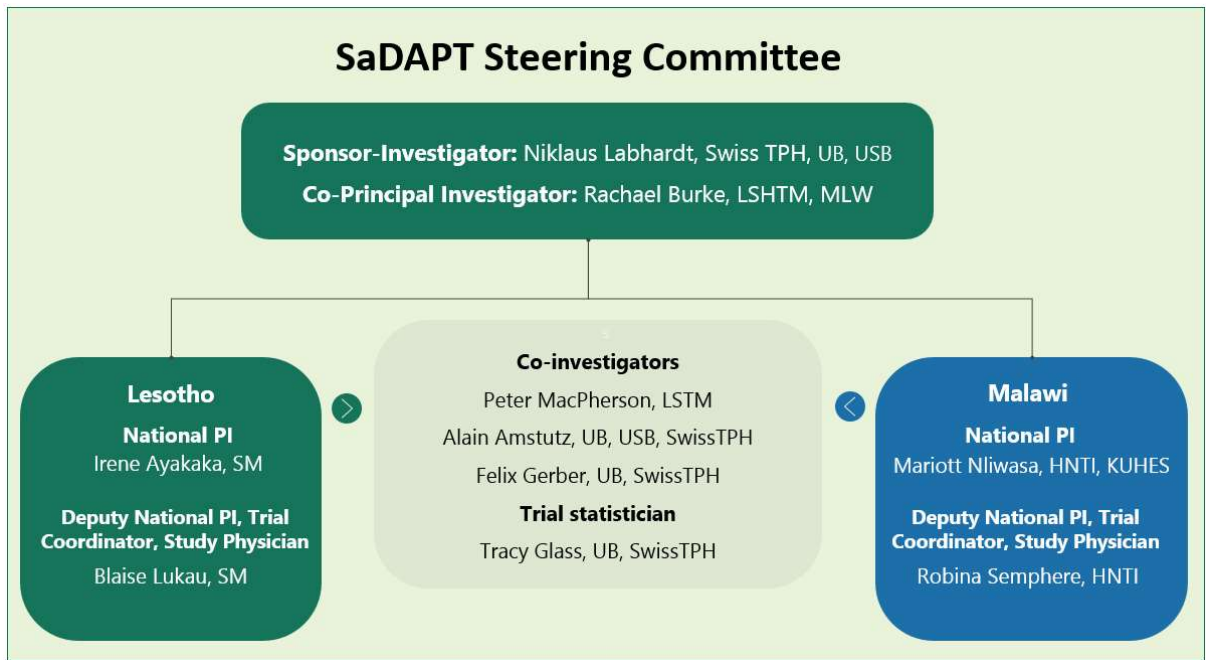


Figure 3 Organogram of the SaDAPT steering committee. HNTI: Helse Nord Tuberculosis Initiative, KUHES: Kamuzu University of Health Sciences, LSHTM: London School of Hygiene and Tropical Medicine, LSTM: Liverpool School of Tropical Medicine, MLW: Malawi Liverpool Wellcome, SwissTPH: Swiss Tropical and Public Health Institute, UB: University of Basel, USB: University Hospital Basel, Switzerland

11 ETHICAL CONSIDERATIONS

11.1 Independent Ethics Committee (IEC)

Ethics approval will be sought from the National Health Research and Ethics Committee of Lesotho, the College of Medicine Research and Ethics Committee (COMREC) of Malawi and the “Ethikkommission Nordwest- und Zentralschweiz” (EKNZ) in Switzerland and the trial will only commence once all three IECs have awarded approval.

Any modifications to the protocol which may impact on the conduct of the study, potential benefit to the patient or patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects, will require a formal amendment to the protocol and will be submitted to the relevant IECs.

At the end of the trial, a written report will be submitted to all involved IECs.

11.2 Evaluation of the risk-benefit ratio

The group-specific timing for ART initiation relative to TB investigations has the following risks and benefits: In the “ART first” arm, the risk of IRIS is increased due to the earlier initiation of ART¹¹ whereas the risk of pre-ART attrition from care and thereby of AIDS-related complications, is minimized²⁰ and the opposite is true for the “TB results first” arm. For an in-depth risk-benefit assessment, we refer to the current WHO HIV guidelines³ and the systematic review conducted to inform them on the question of when ART should be initiated in PLHIV with presumptive TB.¹⁶ The rationale for the conduction of this trial is that based on the current evidence it remains unclear which of the strategies entails a more favorable overall risk-benefit profile.

11.3 Participant information and consent

Prior to enrolment, patients will be asked for written informed consent (or assent with guardian consent in the case of adolescents with age 12 to 17 years) by trained site investigators.

Only individuals who are willing and able to consent will be recruited. We will not recruit incapacitated participants. We will recruit patients who are moderately unwell but retain capacity to consent to trial participation and whose medical care will be managed at primary care (i.e. not requiring transfer to higher level healthcare facility). All study staff taking consent will receive training in GCP and informed consent. Written information will be provided in English and Chichewa (Malawi) or Sesotho (Lesotho) and trained study staff will discuss the trial and answer questions in English, Chichewa or Sesotho. For participants who are illiterate, study staff will orally explain the participant information leaflet to the potential participant in detail in presence of an impartial witness. Illiterate participants will confirm informed consent with a thumbprint, countersigned by an impartial witness. No proxy consent for adults will be sought.

We will also include adolescents (age 12 to 17 years) in the trial. All study staff will receive training in working with and consenting adolescents. We will only recruit adolescents who are both willing and able to assent and who have a guardian (over 18 years) present who is willing and able to provide informed consent. We will not recruit incapacitated adolescents or adolescents who attend without a guardian. Written information to the adult guardian and the adolescent participant will be provided in English, Chichewa or Sesotho and be explained orally in detail to illiterate individuals in presence of an impartial witness. As above, guardian consent and adolescent assent will either be written with a signature, or a thumbprint countersigned by an impartial witness.

All potential participants will receive HIV and TB care from the clinic, according to national guidelines and supervised by national ART and TB treatment providers, irrespective of participation in the trial. Participants are free to withdraw their consent at any time and will continue to receive care as usual.

11.4 Registration of clinical trial

The trial will be registered at ClinicalTrials.gov and a summary of the protocol published in a peer-reviewed journal.

11.5 Participant confidentiality

The investigators will ensure that the participants' confidentiality will be maintained at all times during and after the trial, following procedures outlined in section 6.1 (enrolment procedures) and section 8 (data management).

11.6 Participants requiring particular protection

We will include adolescents aged 12 to 17 years in the trial if guardian consent is provided. Rationale for this and management of special protection is outlined in section 3.2. Compared to other age groups, adolescents have unfavorable HIV outcomes with increased attrition from care at all steps of the care cascade.⁵⁷ They might thus particularly benefit from access to uncomplicated, rapid initiation of ART. There exist no indications that one of the two approaches towards ART initiation applied in this trial might lead to unfavorable outcomes in adolescents.

11.7 Damage coverage

In the event of study-related damage or injuries, the liability of the insurance of the Swiss Tropical and Public Health institute provides compensation, except for claims that arise from participants' misconduct or gross negligence.

11.8 Participant compensation

Participants will participate in the trial in the course of their usual clinic visits, so should incur no extra costs related to transport and a minimal time burden. DBS collection at baseline may cause minimal discomfort.

In Lesotho, no compensation will be paid to participants. In Malawi, \$10 equivalent in Malawi kwacha will be paid to participants.

12 QUALITY CONTROL AND QUALITY ASSURANCE: DESCRIPTION OF MEASURES

12.1 Risk management and possible constraints

12.1.1 Risks to viability of the study

We do not anticipate any serious threats to the study. Potential issues that we will navigate is the COVID-19 pandemic, which may reduce the number of people presenting to clinics and/or lead to change in dispensing and documentation practices. Another issue is lower than anticipated recruitment. If sample size is not reached after the anticipated 12 months recruitment period, we foresee a prolongation of recruitment at sites to be defined.

12.1.2 Risks and benefits for participants

Risks for participants are relatively small. Based on existing evidence, there is equipoise between the two interventions, as outlined in section 2 (background), section 0 (safety) and section 11 (ethics).

Apart from the group-specific timing of ART initiation, participation in the SaDAPT trial will not influence the care that participants receive at the study sites by routine clinical staff. Participants will be encouraged to return to the study clinic any time during the follow-up period to have medical complaints investigated and to receive care, as per local standards. The tracing of participants to ascertain the study endpoint between week 31 and 40 will be used to re-link participants to care and will thus help to minimize the number of participants lost to potentially life-saving HIV care.

The evidence that we aim to generate with this trial may help to establish the optimal approach to ART initiation in this large subgroup of PLHIV and has thus the potential to significantly improve health outcomes of these patients in the future.

12.2 Monitoring and Auditing

The Swiss TPH's Clinical Operations Unit (COU) will be responsible for developing the monitoring strategy. A monitoring plan will be developed before the study start. The monitoring will entail a systematic examination of study related activities and documents. Onsite monitoring in Lesotho will be conducted by a local monitoring team under the supervision of the COU. Onsite monitoring in Malawi will be conducted by the Malawi Liverpool Wellcome Clinical Research Support Unit (CRSU) in accordance with the monitoring plan provided by COU.

At least one monitoring visit at selected sites in both study countries will assess whether the study activities were conducted, and data were recorded, analyzed and accurately reported according to the approved protocol, GCP, and the applicable regulatory requirements.

The study documentation and the source data will be accessible to the monitoring team, the IECs and regulatory authorities upon request. The investigators will assist the inspectors in their duties, if requested.

All involved parties must keep the participant data strictly confidential.

12.3 Translations - Reference language

The reference language of the study documents is English, official language in both study countries. Whereas in both countries, healthcare professionals and thus all study staff is fluent in written and spoken English, this may not be the case for all participants. Therefore, the informed consent forms (ICFs) will be translated from an English master document into the local languages Sesotho (for Lesotho) and Chichewa (for Malawi) while all other study documents will be available in English exclusively. The quality of translation of the ICFs will be ensured by back-translation as well as by quality and comprehension checks by bilingual individuals not involved in the translation.

12.4 Storage of biological material and related health data

We will collect plasma tubes and DBS samples at enrolment for storage and subsequent analysis including HIV genotyping, resistance testing or other related research purposes. The samples collected in Lesotho will be stored for a maximum of five years at the laboratory of Seboche Hospital. All samples collected in Lesotho fall under the biobank agreement (“Biobanking regulations, v2.0”) approved by the ethics committees in Lesotho and Switzerland.

In Malawi samples will be held for up to five years at the TB laboratory Kamuzu University of Health Sciences for studies related to same day ART or TB screening. Samples will remain the property of the government of Malawi. Participants will be asked to consent to samples being transferred out of Malawi for tests not available in Malawi. For instance, we plan to test for HIV genetic resistance – we are hopeful that by the end of the study this will be available in Malawi. However, should this not be the case we will apply for a Material Transfer Agreement (MTA) for shipping.

12.5 Project timeline

<i>Quarter of year</i>	2022				2023				2024			
<i>Quarter of year</i>	1	2	3	4	1	2	3	4	1	2	3	4
Preparation of study protocol, agreement, ethics approval, briefing of stakeholders, logistics preparation, recruitment of staff	x	x										
Recruitment of participants		x	x	x	x	x*	x*					
Follow-up period including tracing		x	x	x	x	x	x	x	x	x*	x*	
Primary endpoint assessment				x	x	x	x	x	x*	x*		
Data analysis, writing of publication										x	x	x

* If extension of recruitment period required to reach sample size

13 FUNDING

This trial is funded by a grant from the Swiss National Science Foundation (Project Number 32003B_205053/1), obtained by the Sponsor-Investigator Niklaus Labhardt. We attest that there is no conflict of interest and that this study will be conducted independently of outside influences in terms of specific intellectual, financial, and proprietary agendas. The funding source will have no role in the design of the trial, and will not be involved in data collection, data analysis, interpretation of the results, and writing of the manuscript.

14 DISSEMINATION OF RESULTS AND PUBLICATION POLICY

14.1 Dissemination to scientific community; including lead in publications

International scientific conferences and publications in scientific peer-reviewed journals will serve for wider dissemination of results. The requirements of the CONSORT statement⁴⁶ will be fulfilled. The study will be registered on ClinicalTrials.gov prior to the start of the trial and a summary of the study protocol will be published in a peer-reviewed journal. The current version of the International Committee of Medical Journal Editors (ICMJE) recommendations is applicable regarding authorship eligibility.⁵⁹ The use of professional writers is not intended.

An anonymized dataset of the study will be deposited at a public data repository once main-findings have been published.

14.2 Information of community and policy makers

Results of this study will be shared with stakeholders at district and national level in both study countries. In Lesotho, health care workers and stakeholders will be informed about the findings during district meetings headed by the District Health Management Team (DHMT) and at national level, the national research symposium of the Ministry of Health will serve as a platform to share the results and discuss their implications among the policy makers. In Malawi, results will be shared with the Blantyre District Health Office, the Department of HIV/AIDS and relevant HIV providing partners.

We will also organise results dissemination events in participating health facilities for staff and patients to hear the results of the study they participated in.

15 ART INITIATION COHORT SUB-STUDY

In parallel to the SaDAPT trial, we will observationally follow-up all PLHIV (re)initiating ART at the study sites in a prospective ART initiation cohort, independent of whether they are eligible for participation in the SaDAPT trial.

15.1 Rationale

The SaDAPT trial enrolls PLHIV (re)initiating ART who present with symptoms of a presumptive TB infection according to W4SS.⁴ However, the sensitivity and specificity of the W4SS for TB case finding in PLHIV is limited and a considerable proportion of PLHIV are known to have subclinical TB disease before initiating ART.^{4,60,61} It is unclear how relevant presence or absence of TB symptoms are for clinical management and outcomes, including occurrence of active TB.⁶² Enrolling all PLHIV (re)initiating ART at the study facilities into an observational cohort in parallel to the recruitment for the SaDAPT trial shall allow to understand if and if yes to what extent characteristics and outcomes among PLHIV with and without TB symptoms who are (re)initiating ART differ and thus also help to weigh external validity and generalizability of the SaDAPT trial results.

15.2 Objectives

The objectives of the ART initiation cohort are to provide a description of baseline characteristics and outcomes of PLHIV (re)initiating ART in primary and secondary health facilities in Blantyre district, Malawi and Lesotho and to allow for an informal comparison between PLHIV (re)initiating ART with and without presumptive TB according to the W4SS. A further objective is to explore and describe the diagnostics, treatment and outcome of PLHIV with presumptive TB not eligible for participation in the SaDAPT RCT (i.e. due to reported pregnancy, signs of CNS disease or positive CrAg test) in routine care in primary and secondary health facilities in Blantyre district, Malawi and Lesotho. The ART initiation cohort will provide insights into the current management and outcomes of PLHIV (re)initiating ART in Malawi and Lesotho beyond the narrow question about timing of ART initiation in presumptive TB addressed with the SaDAPT RCT. The ART initiation cohort's objectives are thus not directly linked to the SaDAPT RCT's objectives, but add to them.

15.3 Study design and duration

The ART initiation cohort is an observational, prospective cohort study. Enrolment period for the ART initiation cohort is identical to the one for SaDAPT RCT, thus starting in June 2022 and ending when sample size for the SaDAPT RCT has been reached approximately 12 months later. Follow-up for the ART initiation cohort is maximum 24 months.

15.4 Study population and rationale

15.4.1 Inclusion and exclusion criteria

PLHIV (re)initiating ART at one of the study facilities during the recruitment period of the SaDAPT RCT meeting the following criteria will be included in the ART initiation cohort:

Inclusion criteria

- 12 years or older
- HIV-positive
- Not taking ART (naïve or reported no ART intake since 90 days or more)
- Planning to continue care at the study facility for at least 30 weeks
- Willing and able to consent (age 18 years or older) or assent with guardian consent (age 12-17 years)

Exclusion criteria

- Medical condition requiring referral to a higher level health facility at enrolment

The ART initiation cohort consists of consenting ART (re)initiators at the study sites, independent of whether they have presumptive TB or whether other exclusion criteria of the SaDAPT trial are present. Participants of the SaDAPT trial are part of the ART initiation cohort. The SaDAPT RCT ends after a follow-up period of maximum 40 weeks with the assessment of the trial's primary endpoint. After the termination of the follow-up of the randomized-controlled intervention, the participants of the SaDAPT RCT, will remain in care at the study facility and will be followed-up observationally like the other participants of the ART initiation cohort that were not part of the SaDAPT RCT.

15.4.2 Estimated sample size

No sample size calculations are performed. The enrolment will last until sample size for the SaDAPT RCT has been reached. We estimate the prevalence of any TB symptom among PLHIV (re)initiating ART between 30%-45%³⁶, thus sample size is estimated to reach between 1300 and 1800 participants.

15.5 Study procedures

Enrolment and follow-up of the ART initiation cohort will be performed by the study staff that is responsible for implementation of the SaDAPT trial, using the same data collection tool.

15.5.1 Screening and informed consent

The screening and informed consent process for the ART initiation cohort will follow the same principles as the processes for the SaDAPT trial and will be conducted by the same site investigators: Potential participants will be approached by a site investigator and asked to give verbal consent to study screening (equivalent to SaDAPT trial screening). As a result of the study screening, individuals will be classified either as not being eligible for any study, as being eligible for the ART initiation cohort only, but not for the SaDAPT trial or as being eligible for the SaDAPT trial (and therefore also for the ART initiation cohort). Individuals meeting the criteria for participation in the SaDAPT trial, will be approached for informed consent for participation in the SaDAPT trial. The SaDAPT trial consent includes consent to further observational follow-up within the ART initiation cohort after termination of the SaDAPT follow-up period.

Individuals meeting the criteria for participation in the ART initiation cohort, but who do not meet the criteria for participation in the SaDAPT trial (for example due to absence of TB symptoms or due to a positive CrAg test) or who refuse participation in the SaDAPT trial, are being approached for consent to participate in the ART initiation cohort. As for the SaDAPT trial, the site investigator will discuss the cohort study with individuals identified as potential participants (and their guardian if age 12-17 years). An ART initiation cohort-specific information leaflet will be provided and all possible questions will be answered before the specific ICF may be signed. Consideration will be given to ensuring privacy and confidentiality. See section 11.3 for information about informed consent process, including for vulnerable participants as the same procedures apply for the ART initiation cohort

15.5.2 Baseline assessment

Enrolment will take place in an environment as private as possible, within the constraints of the clinic setting, so that confidentiality can be assured.

On enrolment, the following procedures will be performed:

- Brief clinical history and physical examination including:
 - o HIV, ART and TB clinical history
 - o Sociodemographic characteristics, health status, comorbidities and co-medications
 - o Measurement of height and weight with determination of BMI and vital signs
 - o Pregnancy status
 - o Screening for signs of CNS disease
- Collection of DBS

15.5.3 ART initiation

Routine staff will decide on timing of ART initiation depending on clinical situation and following national guidelines.^{28,29} Study staff will document the date of ART initiation and relevant circumstances.

15.5.4 Follow-up

HIV care will be provided by routine clinic staff, according to national guidelines^{28,29} with no intervening of study staff.

Study staff will document date of ART initiation, dates and results of possible TB investigations, dates of ART refills, dates and results of VLs and information about possible relevant complications based on data recorded by routine staff in the respective clinical registries. Additionally, a subsample of participants might be contacted by the study team at different points in time during routine clinic visits, via phone calls or via home visits to ascertain their outcome and ask about possible SAEs since enrolment. For participants without a documented VL taken by routine staff six or twelve months after enrolment, a DBS sample may be collected by study staff.

15.6 Safety considerations

The ART initiation cohort does not entail any intervention; all routine ART and TB services will remain as usual. Thus, no AE is likely to be related to study participation.

AEs will be solicited and recorded in the same way as for members of the SaDAPT trial. As all AEs are likely to be unrelated to study participation they do not need to be reported. Deaths should be reported as for the SaDAPT trial (section 7.1.6).

No monitoring, no DSMB and no formal interim analysis are planned for the ART initiation cohort.

15.7 Data management

For data management, data safety and confidentiality, the same procedures apply as for the SaDAPT trial (see section 8).

15.8 Statistics

Cohort baseline characteristics and outcomes will be presented descriptively, no formal statistical analysis will be performed.

15.9 Ethical considerations

15.9.1 Risk benefit assessment and compensation

The ART initiation cohort is purely observational. Risk from participation is minimal. Data confidentiality will be maintained. Participants may benefit from improved care through signposting of missing HIV and/or TB drug prescription for eligible participants to routine staff and through re-linkage to care during the tracing of participants lost to follow-up. The evidence generated with this cohort study will contribute valuable evidence to the understanding of current management and outcomes of PLHIV (re)initiating ART in southern Africa. Participants in Malawi will receive a compensation of 1000 Malawi kwacha (circa 1.25 US dollar), no compensation will be paid to participants in Lesotho.

15.9.2 Rationale for inclusion of vulnerable subjects

We will include adolescents aged 12 to 17 years if assent and guardian consent is provided and consenting pregnant women in the ART initiation cohort. Both groups are often excluded from interventional studies due to safety or ethical concerns. Evidence on these subgroups to improve treatment approaches is required as for all other PLHIV. We will include them in this observational study, to generate some evidence on current management and outcomes of these specific subgroups of PLHIV without exposing them to the risk of an intervention.

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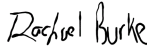
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