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Feasibility of implementing the advanced HIV disease care package as part of community-based HIV/TB activities: a mixed-methods study protocol

Tinne Gils ,[1] Lutgarde Lynen,[1] Josephine Muhairwe,[2,3] Kamele Mashaete,[2] Thabo Ishmael Lejone,[2] Philip Joseph,[4] Thulani Ngubane,[4] Alfred Kipyegon Keter,[1] Klaus Reither,[5,6] Alastair van Heerden[4,7]

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For numbered affiliations see end of article.

Correspondence to
Tinne Gils; tinnegils@gmail.com

ABSTRACT

Introduction Although the advanced HIV disease (AHD) care package reduces morbidity and mortality in people with AHD (defined in people living with HIV as WHO stage 3 or 4, CD4 count <200 cells/µL or age <5 years), it is barely implemented in many countries. A novel point-of-care CD4 test rapidly identifies AHD. We evaluate the feasibility of implementing the AHD care package as part of community-based HIV/tuberculosis services.

Methods and analysis This two-phased study is guided by the Medical Research Council framework for evaluation of complex interventions. Stage 1 is a stakeholder consultation to define tools and indicators to assess feasibility of the AHD care package. Stage 2 is the implementation of the AHD care package during a facility-based tuberculosis diagnostic accuracy study in high-burden HIV/tuberculosis settings. Consenting adults with tuberculosis symptoms in two sites in Lesotho and South Africa are eligible for inclusion. HIV-positive participants are included in the feasibility study and are offered a CD4 test, a tuberculosis-lipoarabinomannan assay and those with CD4 count of ≤200 cells/µL a cryptococcal antigen lateral flow assay. Participants are referred for clinical management following national guidelines. The evaluation includes group discussions, participant observation (qualitative strand) and a semistructured questionnaire to assess acceptability among implementers. The quantitative strand also evaluates process compliance (process rating and process cascade) and early outcomes (vital and treatment status after twelve weeks). Thematic content analysis, descriptive statistics and data triangulation will be performed.

Ethics and dissemination The National Health Research and Ethics Committee, Lesotho, the Human Sciences Research Council Research Ethics Committee and Provincial Department of Health, South Africa and the Ethikkommission Nordwest- und Zentralschweiz, Switzerland, approved the protocol. Dissemination will happen locally and internationally at scientific conferences and in peer-reviewed journals.

Trial registration number NCT04666311.

Strengths and limitations of this study

- This mixed-method study will be the first to evaluate the feasibility of implementation of the advanced HIV care package, including a novel point-of-care CD4 test.
- The study is embedded in a multicountry tuberculosis (TB) diagnostic accuracy study conducted in two sites in high-burden HIV/TB settings.
- The qualitative and quantitative tools for this study are prepared through extensive consultation with field staff, academic and programme experts.
- Convergent and holistic triangulation will be applied to data from semistructured questionnaires, group discussions, participant observation, process and early outcome evaluation.
- Due to COVID-19-related restrictions, the stakeholder consultation and part of the qualitative data collection are conducted online.

INTRODUCTION

Globally, AIDS-related deaths declined by 61% since 2004 due to the availability of HIV testing, antiretroviral treatment (ART) and early ART initiation.[1] Unfortunately the HIV epidemic is far from over, with 690 000 (480 000–1 million) people living with HIV (PLHIV) dying from AIDS-related illness in 2020.[1] Patients who present to, or re-enter care with advanced HIV disease (AHD) are at high risk of opportunistic infections and death, with a higher risk when immunity is lower.[2] AHD is defined as present in PLHIV when having a WHO stage of 3 or 4 condition, a CD4 +T cells (CD4) count below 200 cells/µL or being a child <5 years old.[3] AHD is common in sub-Saharan Africa, with studies reporting between 32% and 71% of patients initiating care with AHD, and up to 60% patients presenting with AHD after disengagement.[4–6] When initiating ART with AHD, patients have an estimated 17% risk of mortality within 1 year.[7 8] AHD requires prompt medical attention with up to 25% of patients with AHD with previous ART exposure dying within 48 hours of hospital admission.[5]

Table 1 Overview of advanced HIV disease care package

	Intervention	CD4 cell count
Screening and diagnosis	CD4 cell count Four symptom screen, chest X-ray, C-reactive protein	Any
	Molecular rapid diagnostic if TB screening positive*	Any
	LF-LAM screening	≤200 cells/µL (inpatient)/≤100 cells/µL (outpatient)/ any if TB symptoms or seriously ill†
	CrAg screening	≤100 cells/µL/considered if ≤200 cells/µL
Prophylaxis/pre-emptive treatment	Co-trimoxazole prophylaxis	<350 cells/µL/ WHO stage 3 or 4/any if high prevalence of malaria or SBI
	TB preventive treatment	Any
	Fluconazole pre-emptive therapy for CrAg-positive people without evidence of meningitis	≤100 cells/µL
ART initiation	Rapid ART initiation	Any
	Defer initiation if clinical symptoms suggest meningitis (TB or cryptococcal)	Any
Adherence support	Tailored counselling to support optimal adherence to the AHD care package, including home visits if feasible	CD4 <200 cells/µL

Adapted from WHO.[13]
*WHO TB symptom screen includes presence of fever, weight loss or any cough. People living with HIV may present with signs or symptoms of extrapulmonary TB also including lymphadenopathy, meningitis or other atypical presentations warranting evaluation.
†Seriously ill is defined based on four danger signs: respiratory rate >30/min, temperature >39°C, heart rate >120/min and unable to walk unaided.
AHD, advanced HIV disease; ART, antiretroviral therapy; CrAg, cryptococcal antigen; LF-LAM, lateral flow lipoarabinomannan assay; SBI, severe bacterial infections (including bloodstream, respiratory, central nervous system and gastrointestinal infections); TB, tuberculosis; WHO, World Health Organization.

Tuberculosis (TB), cryptococcal meningitis and severe bacterial infections are WHO stage 3 and 4 conditions that cause more than half of deaths among PLHIV.[7 9] TB is the leading cause of AIDS-related deaths globally and its contribution is likely underestimated.[10] In hospitals in resource-limited settings, TB remained undiagnosed at death in almost half (45%) of HIV-positive TB cases.[11] Cryptococcal meningitis accounts for 15% of AIDS-related deaths globally, and 73% of prevalent cases are in sub-Saharan Africa.[12]

Since 2017, WHO recommends a package of interventions to manage AHD, including screening, treatment and/or prophylaxis for opportunistic infections, rapid ART initiation and intensified adherence support for those identified with AHD (table 1).[3 13] This recommendation is based on evidence of the capacity of the package components to reduce morbidity and mortality among people with AHD.[14–16] In absence of clinical indication of WHO stage 3 or 4 disease, a CD4 count of 200 cells/µL or less is the entry criterion to start the AHD care package in adults. When identified, AHD triggers screening for *Mycobacterium tuberculosis* lipoarabinomannan antigen (TB LAM) and cryptococcal antigen (CrAg) by use of point-of-care TB LAM and CrAg lateral flow assays, with patient management depending on results.[3] In all HIV-positive patients with symptoms of TB, a sputum Xpert MTB/RIF assay should be performed, along with a TB LAM test regardless of CD4 count.[2 13 17]

The availability of point-of-care diagnostics, in addition to HIV tests, is thus essential for successful implementation of the AHD care package in primary care facilities. However, since the introduction of universal Test and Treat, CD4 measurement tests are no longer commonly available at primary care level.[3 4] Moreover, TB LAM and CrAg lateral flow assays are not widely available in most low-income and middle-income settings. Consequently, the AHD care package is barely implemented.[4] When present, the AHD care package is often only available to study populations and/or selected sites supported by international organisations.[4 18]

The novel Omega VISITECT CD4 Advanced Disease Lateral Flow Assay (Omega Diagnostics, Scotland, UK; VISITECT CD4 LFA), is the first disposable point-of-care test, which allows visual interpretation of a result of above or below 200 CD4 cells/µL.[19] The test had an acceptable diagnostic accuracy when performed by laboratory technicians on venous blood (sensitivity: 94.6 %, specificity: 81.7%), and when performed by clinicians on finger-prick samples (sensitivity: 98.3%, specificity 77.2%).[19] The test is also feasible and easy-to-use according to healthcare workers.[19 20]

Box 1 Phases of framework for complex intervention

Phase 0: Theory development: Identify the evidence base to select the appropriate intervention and identify and develop appropriate theory to develop the intervention.
Phase I: Formative stage: Identify the components of the intervention and the underlying mechanisms by which they will influence outcomes and link emerging perceptions to process indicators and outcomes indicators
Phase II: Assessing feasibility and piloting methods: Test procedures for compliance, acceptability and intervention delivery.
Phase III: Evaluation of the intervention: Study effectiveness of a fully defined intervention, ideally comparing with an appropriate alternative, using a protocol that is theoretically defensible, reproducible and adequately controlled in a study with appropriate statistical power.
Phase IV: Implementation: Determine whether others can reliably replicate your intervention and results in uncontrolled settings over the long term

Adapted from Campbell *et al*.[22]

There are limited data on feasibility of AHD care package implementation, and on use of VISITECT CD4 LFA to identify AHD.[2 4] We integrate the AHD care package, including VISITECT CD4 LFA, into procedures of a prospective TB diagnostic accuracy study. We aim to evaluate the feasibility of implementing the AHD care package, including VISITECT CD4 LFA as part of community-based HIV/TB activities.

METHODS AND ANALYSIS

The Medical Research Council Framework for complex interventions

The intervention of introducing the AHD care package in community-based HIV/TB-programmes is considered complex, that is, contains several interacting components. The Medical Research Council framework is used for evaluation of this intervention (box 1).[21 22]

The content and benefits of the AHD care package are well defined and WHO recommended. Phase 0 is thus considered as accomplished.[3] To assess the feasibility of implementing the AHD care package as part of community-based HIV/TB activities, we focused on phase I and phase II of the framework. This evaluation involves an iterative, cyclical course with multiple feedback loops, and integrates quantitative and qualitative methods. Phase III and IV have currently not been planned.

Objectives

The general objective is to evaluate the feasibility of implementing the AHD care package, including the novel VISITECT CD4 LFA, for implementation as part of community-based HIV/TB activities. The evaluation takes place in health facilities during a prospective diagnostic accuracy study and assesses the potential for implementation of the AHD care package in future community activities. The community-based HIV/TB activities could include interventions for prevention, diagnosis, treatment and/or care for HIV and/or TB taking place in the community, that is, not inside a health facility. The main research questions we address are:

- How is the AHD package implemented during a facility-based TB diagnostic accuracy study?
- Can the AHD care package be implemented as part of community-based HIV/TB activities?
- What is the best way to implement the AHD care package during community-based HIV/TB activities?

Among aspects of feasibility to be evaluated were acceptability among implementers, adherence to process flow and timing, and early outcomes.[23]

The sub-objectives per stage are:

Stage I

- Develop indicators and tools for evaluation of feasibility (acceptability, process, early outcomes) of implementation of the AHD care package including the novel VISITECT CD4 LFA.
- Evaluate and adjust draft materials for training and implementation support.

Stage II

- Evaluate the implementation process and early outcomes, identify barriers to implementation and possible solutions.
- Evaluate acceptability among implementers and identify necessary roles and responsibilities for implementation.
- Evaluate and adjust materials for training and implementation support.

Cross cutting objectives are to assess whether the feasibility of implementing the AHD care package differs according to the setting and its prevalence of detected AHD, and whether the feasibility is affected by the COVID-19 pandemic.

Study design

This is a two-site prospective study in two stages with a multi-strand (qualitative and quantitative), mixed-method multiphase design (figure 1). The two stages correspond to phases I and II of evaluation by the Medical Research Council. Stage I and II are sequential in time and stage I will provide exploratory data to develop tools used in stage II. Stage II includes a quantitative and qualitative strand of equal weight, with concurrent and sequential elements. Emerging data of one element influence the final data collection tools for other elements.

Stage 1

Stage 1 is an exploratory stakeholder consultation to prepare the implementation process, tools to be used, and the choice of evaluation and outcome indicators for stage 2. The process consists of information sharing, feedback loops and group discussions with iterative feedback.

Stage 2

Stage 2 is a feasibility study with a quantitative and a qualitative strand. The quantitative strand includes a process

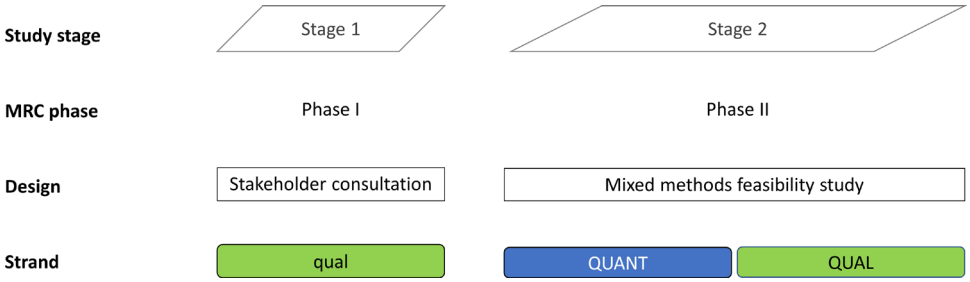

Figure 1 Diagram of study stages and methods. The strands include an exploratory qualitative strand with lower weight, followed by a quantitative and a qualitative parallel strand with equal weight. MRC, Medical Research Council; qual, qualitative; quant, quantitative.

cascade with data gathered during and in parallel with data collection of the diagnostic accuracy study, a semi-quantitative rating of process steps, evaluation of early outcomes and assessment of feasibility indicators by means of a semistructured questionnaire. The qualitative strand includes participant observation by an expert evaluator and group discussions with implementers of the AHD care package. Data collection tools for qualitative and quantitative analysis can be adapted with emerging information from previous assessments.

Study setting

The stakeholder analysis is held online. The feasibility assessment takes place in two outpatient sites in South Africa and Lesotho and partly online.

South Africa

In South Africa in 2019, adult HIV prevalence was estimated at 19.0% (12.1%–24.7%), and incidence at 7.79 (4.58–10.80) per 1000 population. There were an estimated 84 000 (43 000–150 000) deaths of AIDS in 2019, with 36 000 attributed to TB. Thirty-one per cent of patients had a CD4 count of <200 cells/µL at diagnosis in the same year.[24] The study is conducted in a mobile clinic outside Caluza Primary Healthcare facility in Pietermaritzburg, KwaZulu-Natal province, South Africa.

Lesotho

In Lesotho in 2019, the adult HIV prevalence was estimated at 21.8% (20.3%–21.9%), 8600 (6300–9800) were newly infected and 4600 (3800–6100) died, with 3600 deaths attributed to TB. Twenty-four per cent of patients had a CD4 count of <200 cells/µL at diagnosis in the same year.[24] The study is conducted at the premises of Butha-Buthe District Hospital in Northern Lesotho.

The AHD care package within the TB TRIAGE+ ACCURACY trial

All study procedures and samples for TB TRIAGE +ACCURACY including those evaluated in the feasibility study are presented in online supplemental file 1. TB TRIAGE +ACCURACY plans to enrol 1400 participants. While in routine HIV/TB care, the entry point of the AHD care package would typically be a positive HIV status, in TB TRIAGE +ACCURACY, the entry point for patients is TB symptoms, after which an HIV test is done (in case of an unknown HIV status). Participants who are known HIV-positive cases or those who test HIV-positive in TB TRIAGE +ACCURACY are enrolled in the feasibility study. For those participants an Alere Determine TB LAM antigen test (Abbott, USA: Alere TB LAM) in urine is performed, and a serum CrAg lateral flow assay (IMMY, USA) in case of a CD4 count of 200 or less determined by VISITECT CD4 LFA. All patients enrolled in TB TRIAGE +ACCURACY receive a referral letter, including the results from AHD care package tests when applicable, for further follow-up and treatment by their healthcare provider according to national guidelines.[25 26] At 12 (10–14) weeks, patients receive a phone call to inquire about their vital status, TB and ART treatment status, and HIV-positive patients' treatment records are reviewed to determine the state of compliance with national guidelines for AHD care. All procedures restricted to HIV-positive participants are part of the feasibility study.

The impact of COVID-19

The surge of the COVID-19 pandemic since March 2020 led to protocol revisions in the preparatory phase. COVID-19 infection control precautions (masks, hand washing, optimisation of patient flow) were put in place at the study sites. Due to in-country and international travel restrictions, several trainings and the site initiation visits were conducted virtually. The stakeholder analysis, semistructured interviews and group discussions are held online. Assessment of the feasibility of implementing the AHD care package during the pandemic was included in the evaluation. Due to overlapping symptoms of TB and COVID-19, all patients in TB TRIAGE +ACCURACY also receive a novel SARS-Cov-2 antigen rapid diagnostic test, a SARS-Cov-2 real-time PCR test and CAD4COVID, a digital chest X-ray analysis software, in combination with differential white cell count.

Study population and recruitment

Stage 1

The stakeholder consultation is conducted with international experts from the Swiss Tropical and Public Health Institute, the Institute of Tropical Medicine in Belgium, the Human Sciences Research Council in South Africa and SolidarMed in Lesotho, who are all coinvestigators to TB TRIAGE +ACCURACY. In addition, programme

experts from the Human Sciences Research Council and SolidarMed are included.

Stage 2

The mixed-method study includes two study populations: patients and implementers.

Patients

The study population for evaluation of the process cascade and early outcomes are patients. Patients are screened for presence of any TB symptom at outpatient departments of the study sites and in the community. Those with TB symptoms are referred to the study facilities for TB TRIAGE +ACCURACY study procedures. Participants to TB TRIAGE +ACCURACYwho are HIV-positive receive the AHD care package. The following inclusion and exclusion criteria are applied for enrolment in TB TRIAGE +ACCURACY:

Inclusion criteria

- Willing and able to provide signed written consent or witnessed oral consent in the case of illiteracy, prior to undertaking any study-related procedure.
- Adults (≥18 years).
- Any of the cardinal symptoms of TB (cough, weight loss, night sweats, fever) of any duration.

Exclusion criteria

- Pregnancy (based on oral information from participant).
- Any condition for which participation in the study, as judged by the investigator, could compromise the well-being of the subject, or prevent, limit or confound protocol specified assessments.
- Critically sick patients who need immediate medical care.
- Current anti-TB treatment.

Additional inclusion criteria for the feasibility study among those who are enrolled in TB TRIAGE +ACCURACY:

- Previously known HIV-positive or newly tested HIV-positive.

HIV testing is performed according to existing national guidelines.[25 27]

Implementers

The study population for the process rating scale, structured questionnaires and participant observation are all health professionals or lay workers who implement the entire AHD package or parts of it, called the implementers. The expert evaluator, the person who oversees the AHD care package implementation process performs the process rating scale and participant observation and is additionally included in the group discussions. Written consent from participants is conditional to participation in group discussion and semistructured questionnaires.

Outcomes

The overall outcome is establishing the feasibility of implementing the AHD care package, including the VISITECT CD4 LFA, as part of community-based HIV/TB activities in Lesotho and South Africa. Specific outcomes per study stage were broadly defined in this protocol, and stage 1 outcomes are used to further elaborate stage 2 outcomes.

Stage 1

- Indicators and evaluation material on feasibility (including acceptability, process, and early outcomes) to evaluate pilot implementation.
- Training materials, standard operating procedures, job aids and other tools for implementation of the AHD care package.

Stage 2

Outcomes for the mixed-method study include qualitative and quantitative outcomes.

Qualitative outcomes

- Perceptions of implementers on feasibility of implementing the AHD care package during a facility-based TB diagnostic accuracy trial, as part of community HIV/TB activities, and during the COVID-19 pandemic.
- Perceptions of implementers on acceptability and feasibility of implementing the AHD care package for patients and for other healthcare workers.
- Barriers to and enablers for successful implementation.
- Requirements, roles and responsibilities of implementers.

Quantitative outcomes

- Feasibility and acceptability among implementers (proportions of answers to semistructured questionnaires).
- Process compliance (median scores on process rating scale, proportions of process steps fulfilled and timing of different steps).
- Early outcomes (vital status and proportion of patients for whom the AHD procedure led to the correct medical follow-up according to national guidelines after 12 weeks).

Data collection

Figure 2 presents an overview of data collection procedures in time and study populations.

Stage 1

The lead researcher performs a literature review and drafts indicators for feasibility, including acceptability and process, early outcomes and data collection tools. The lead researcher also drafts standard operating procedures, training materials and job aids for implementation. All drafts are shared electronically with the academic and programmatic experts accompanied by open and structured questions) aimed at identifying participants' preferences for certain indicators and the reasons why. Several drafts are shared, and adapted after feedback, through an iterative process. The process of semistructured feedback is complemented with online interviews with team members, to further explore anticipated barriers to

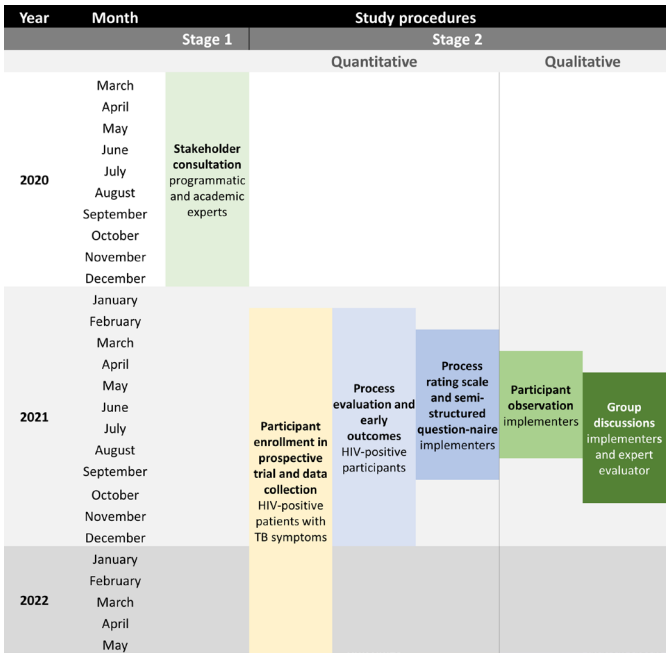

Figure 2 Overview of study procedures and population.

implementation, based on emerging themes from the questionnaires. An analytical memo is kept, detailing the dates, participants and outcomes of discussions and the decisions made.

Stage 2

Process cascade

Data on the different procedural steps and their outcomes are collected prospectively in MACRO trial software (MACRO V.4.8.1, Elsevier) during the cohort study. These data will be exported to Microsoft Excel to construct the process cascade.

Early outcomes

At 12 (10–14) weeks after enrolment, nurses within study teams conduct phone calls and extract data from patient records to ascertain their vital and treatment status. The data are entered in the MACRO database and will be exported to Microsoft Excel to construct a database for evaluation of early outcomes after AHD administration.

Semistructured questionnaires

A paper-based semistructured questionnaire, developed in phase I, is administered to all implementers of the AHD care package by the lead researcher. All participants receive an information sheet and sign informed consent before completing the questionnaire. The answers to the questionnaires are encoded in Microsoft Excel. The questionnaire is administered twice, after 3 and 6 months of AHD implementation. The content of the questionnaire for the 6-month evaluation can be adapted following new information that may arise during 3-month data collection.

Process evaluation with rating scale

An assigned expert evaluator from the study team will observe the implementers performing different steps of the AHD care package, monitor and record time spent on each step of the AHD procedure, and evaluate the completeness of the process, using a paper-based checklist with a Likert-type rating scale. The results will be encoded in Microsoft Excel.

Participant observation

To complement the quantitative evaluation with the rating scale, an expert evaluator gathers data resulting from participant observation of the people implementing the AHD care package, during the process. Depending on the situation, these observations may be participative (ie, from strict observation to asking questions during the process). The expert evaluator takes notes on paper during the observations and transcribes summaries of the observations in Microsoft Word documents.

Group discussions

The semistructured questionnaires and participant observations are complemented with group discussions, based on a topic guide developed from emerging themes from stage 1 and the previous steps in phase 2. All participants receive an information sheet and sign an informed consent before participating in the group discussion, including a separate consent for recording. The discussions are held in groups of up to eight people with similar profiles (study team). The lead researcher moderates the discussion online, assisted by an on-site moderator and translator who are united with the study team on site. Group discussions are conducted twice; once per site around 3 months after start of implementation, and once jointly with the implementers physically gathered at one of the sites. The main language is English, but participants can use isiZulu or Sesotho if they wish. The discussions are recorded on audiotape and a summary are transcribed on a Word document after the discussion by a trained and experienced transcriber/translator. A trained notetaker creates a memo describing expressions, gestures and other impressions that are not recordable.

Patient and public involvement

This feasibility study and the trial in which it is embedded was developed in consultation with service providers from Butha-Butha hospital and Caluza clinic, and field teams of SolidarMed and the Human Sciences Research Council. The field teams were direct stakeholders in the definition of study outcomes and study design. The study proposals were presented to the national TB programme in Lesotho and the provincial department of health in KwaZulu-Natal in South Africa. Patients were not directly involved in study design or conduct. However, study results will be disseminated locally to reach communities, including patients, civil society groups, and the wider

public through presentations, local media and information on the websites of SolidarMed and the Human Sciences Research Council.

Data analysis

Quantitative analysis

Analyses will be performed using Stata/IC 16.0 (StataCorp). Participants' (patients and implementers) characteristics and outcomes from structured questionnaires will be summarised using means and SD or medians and IQRs for continuous variables, and frequencies and proportions for categorical data. Frequencies and proportions will also be used for description of the process cascade and early outcomes. Comparisons of means and medians will be done using t-test or nonparametric k-sample tests, respectively. Differences in proportions will be assessed using Pearson's χ^2 tests or Fisher's exact test as appropriate.

Qualitative analysis

We will use an iterative approach, that is, collecting data and analysing through thematic content. Preliminary data will be used for further sampling, analysis and theory building. Formative data will be coded to inform further research questions and method application. Additional participant observation and group discussion may be conducted based on early results. Thematic content analysis will be used to categorise recurrent themes in transcripts of observations and group discussions. All transcripts and memos will be coded and analysed using QSR NVivo V.11 or higher.

Triangulation

We will apply convergent triangulation to validate the data obtained from different research methods and identify convergent results. We will also apply holistic triangulation to identify unique perspectives/angles that one or more of the individual methods can provide. Qualitative and quantitative data will initially be analysed separately as described above. Intermediate emerging information can be used to adapt tools and approach for future data collection (eg, if a missing process step is detected during the prospective cohort data collection, this challenge might be further explored during group discussions). At the end of the study, outcomes emerging from the different methodological strands will be compared for convergent and divergent information.

ETHICS AND DISSEMINATION

This study and the trial in which it is embedded, are being conducted in compliance with the approved protocols, the International Conference on Harmonisation Good Clinical Practice E6 and the current version of the Declaration of Helsinki. This protocol was approved by the National Health Research and Ethics Committee of Lesotho, the Human Sciences Research Council Research Ethics Committee, and the Provincial Department of Health of KwaZulu-Natal in South Africa, and the Ethikkommission Nordwest- und Zentralschweiz in Switzerland. Study implementers and expert evaluators provide written informed consent for participation in the structured questionnaires and group discussions. Patients enrolled in TB TRIAGE +ACCURACY provide informed consent, including for the AHD procedure and data collection. Both informed consent forms were translated in Sesotho and in isiZulu and back translated by a second person for quality control. SolidarMed and the Human Sciences Research Council will disseminate the information produced by this study locally through community advisory boards, provincial, district and national symposia, contacts to civil society groups, local press releases and information on the organisation website. The investigators will inform national health authorities about project results. Internationally, results will be disseminated through meetings with policy makers, publications in peer-reviewed journals, presentations at scientific conferences and through media.

Author affiliations
[1]Clinical Sciences, Institute of Tropical Medicine, Antwerpen, Belgium
[2]SolidarMed, Partnerships for Health, Maseru, Lesotho
[3]Institute of Global Health, University of Geneva, Geneva, Switzerland
[4]Centre for Community Based Research, Human Sciences Research Council, Pietermaritzburg, South Africa
[5]Swiss Tropical and Public Health Institute, Basel, Switzerland
[6]Medical Outpatient Department, University of Basel, Basel, Switzerland
[7]Developmental Pathways for Health Research Unit, University of the Witwatersrand, Johannesburg, South Africa

Contributors TG and LL conceived the study idea. TG, JM, KM, TIL, PJ, TN, AKK and AvH designed the study. AvH, JM and KR supervised study implementation and data acquisition. KM, PJ and TN perform data acquisition and interpretation. TG, LL ad AvH drafted the first version of the manuscript. All authors revised the manuscript and agreed on the final version.

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ORCID iD
Tinne Gils http://orcid.org/0000-0002-5518-9600

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