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Early empiric anti-*Mycobacterium tuberculosis* therapy for sepsis in sub-Saharan Africa: a protocol of a randomised clinical trial

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ABSTRACT

Introduction Sub-Saharan Africa shoulders the highest burden of global sepsis and associated mortality. In high HIV and tuberculosis (TB) prevalent settings such as sub-Saharan Africa, TB is the leading cause of sepsis. However, anti-TB therapy is often delayed and may not achieve adequate blood concentrations in patients with sepsis. Accordingly, this multisite randomised clinical trial aims to determine whether immediate and/or increased dose anti-TB therapy improves 28-day mortality for participants with HIV and sepsis in Tanzania or Uganda.

Methods and analysis This is a phase 3, multisite, open-label, randomised controlled clinical 2×2 factorial superiority trial of (1) immediate initiation of anti-TB therapy and (2) sepsis-specific dose anti-TB therapy in addition to standard of care antibacterials for adults with HIV and sepsis admitted to hospital in Tanzania or Uganda. The primary endpoint is 28-day mortality. A sample size of 436 participants will provide 80% power for testing each of the main effects of timing and dose on 28-day mortality with a two-sided significance level of 5%. The expected main effect for absolute risk reduction is 13% and the expected OR for risk reduction is 1.58.

Ethics and dissemination This clinical trial will determine the optimal content, dosing and timing of antimicrobial therapy for sepsis in high HIV and TB prevalent settings. The study is funded by the National Institutes of Health in the US. Institutional review board approval was conferred by the University of Virginia, the Tanzania National Institute for Medical Research, and the Uganda National Council for Science and Technology. Study results will be published in peer-reviewed journals and in the popular press of Tanzania and Uganda. We will also present our findings to the Community Advisory Boards that we convened during study preparation.

Trial registration number ClinicalTrials.gov (NCT04618198).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The 2×2 factorial design of this pragmatic trial of immediate initiation of anti-tuberculosis (TB) therapy and sepsis-specific dose anti-TB therapy will inform on the optimal content, dosing and timing of antimicrobial therapy for adult sepsis in HIV and TB endemic settings.
⇒ Distinct clinical trial phenotypes coupled with comprehensive molecular evaluation of alternative pathogens of sepsis (by our multiplex Febrile Illness TaqMan Array Card-TAC) will allow for prespecified subgroup analyses of those with confirmed TB.
⇒ A pharmacokinetic (PK) analysis of the subset of participants receiving immediate anti-TB therapy will determine whether sepsis-specific dose anti-TB therapy will significantly increase serum concentrations of rifampin and isoniazid and if those with confirmed TB sepsis and PK parameters within target range have a significantly faster time to clinical improvement.
⇒ This pragmatic trial is endorsed by community advisory board members.
⇒ A limitation of this randomised controlled trial of antimicrobial therapy for adult sepsis in sub-Saharan Africa is lack of blinding.

INTRODUCTION

Sepsis is a syndrome of critical illness defined as life-threatening organ dysfunction due to a dysregulated host response to infection and is the leading cause of global mortality.[1] In 2017, the WHO made sepsis a global health priority.[2] The highest burden of sepsis occurs in low-income and middle-income countries, and specifically in sub-Saharan Africa where there are at least 1.2–2.2 million cases of sepsis and 6.5 million deaths due to infection annually.[3 4] The majority of these patients are living with HIV. Although little is known about sepsis in the global South, we have determined that the leading cause of sepsis in this region is *Mycobacterium tuberculosis*

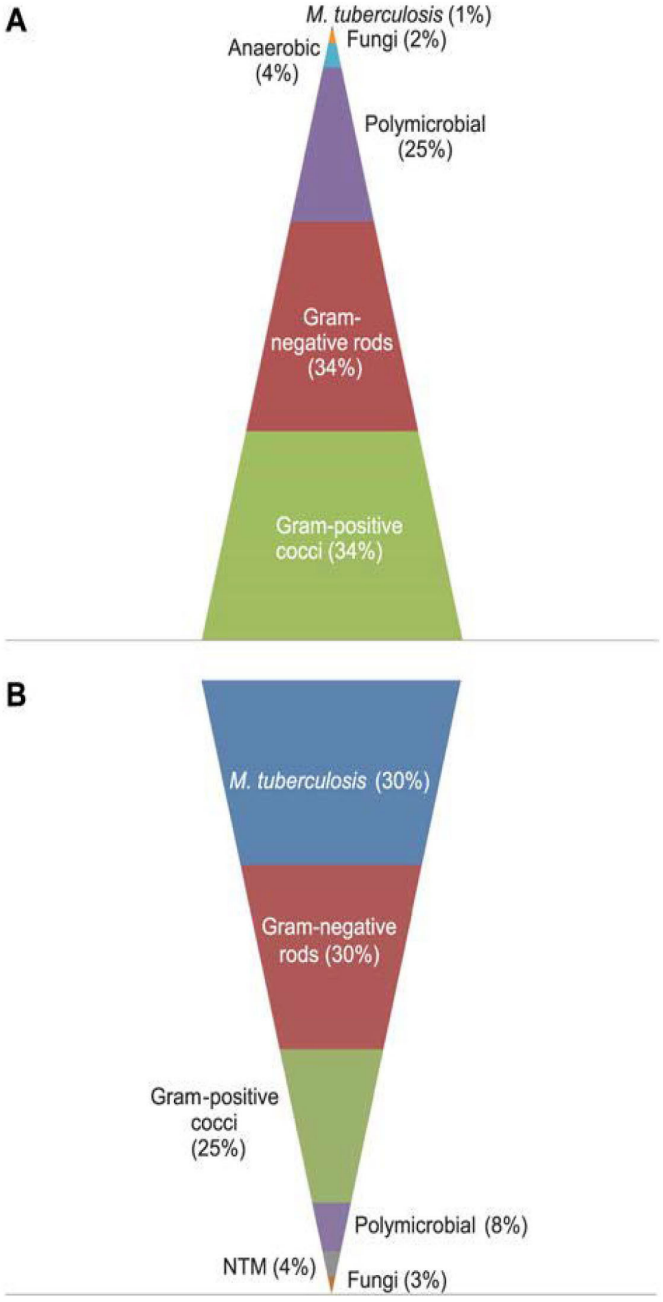

Figure 1 Pyramid figure demonstrating the estimated prevalence of (A) community-acquired bloodstream infections in severely ill adults in industrialised countries versus (B) high TB-HIV burden settings in sub-Saharan Africa. Adapted from Int J Tuberc Lung Dis 2015 Oct;19(10):1128–34 with permission.

(TB), which is responsible for 25%–30% of bloodstream infections in septic patients[5] (figure 1). TB sepsis is associated with 20%–50% case fatality rates with the majority of deaths occurring within the first 4–5 days of hospital admission.[6] However, it is difficult to identify TB sepsis clinically or with diagnostic tests, which are often unavailable and have limited sensitivity. Therefore, TB can be missed and patients with TB sepsis may not receive anti-TB therapy, or if they do, treatment initiation may be delayed.

We found that empirical treatment of TB in septic patients in Uganda without a confirmed diagnosis of TB was associated with improved 28 day mortality.[7] Importantly, however, pharmacokinetics (PK) and pharmacodynamics studies of anti-TB therapy in hospitalised patients have shown low circulating drug concentrations that are suboptimal for microbial kill.[8 9] Therefore, our hypotheses are that immediate anti-TB therapy will improve 28-day mortality compared with anti-TB therapy that is administered only after a diagnosis is made, and that optimised sepsis-specific dosing will improve 28-day mortality compared with conventional WHO recommended weight-based dosing regardless of the timing of administration.

We will test these hypotheses through *A* randomised clinical *Tria**L*** of early empiric *Anti-Mycobacterium tuberculosis* therapy for *S*epsis in sub-Saharan Africa (ATLAS trial). This ATLAS trial is strongly endorsed by Tanzanian and Ugandan community advisory boards and will be the first to determine the optimal content, dosing and timing of the antimicrobial regimen for adult sepsis in sub-Saharan Africa.

METHODS AND ANALYSIS

Study design

The ATLAS trial is a phase 3, multisite, open-label, randomised controlled clinical 2×2 factorial superiority trial of (1) immediate initiation of anti-TB therapy and (2) sepsis-specific dose anti-TB therapy in addition to standard of care antibacterials for adults with HIV and sepsis admitted to our study sites at Kibong'oto Infectious Diseases Hospital in Tanzania or Mbarara Regional Referral Hospital in Uganda (figure 2). The primary endpoint is 28-day mortality and the secondary endpoints include in-hospital mortality, 6-month mortality, time to death, duration of hospitalisation, time to anti-TB therapy, adverse drug events during the 28-day study period, final sepsis aetiology, time to ambulation and temperature normalisation, Karnofsky score, and rifampin and isoniazid peak concentrations (Cmax) and total exposures as determined by the area under the concentration–time curve (AUC 0–24 hours). A sample size of 436 participants will provide 80% power for testing each of the main effects of timing and dose on 28-day mortality with a two-sided significance level of 5%. The expected main effect for absolute risk reduction is 13% and the expected OR for risk reduction is 1.58.

Study population

Study participants will be recruited consecutively from each study site hospital and enrolled if they provide consent, are ≥18 years old, living with HIV, and are found to have sepsis defined as (1) clinical concern for infection, (2) ≥2 modified quick sepsis related organ failure assessment (qSOFA) score criteria including respiratory rate ≥22; GCS score <15; or systolic blood pressure ≤90 or mean arterial pressure ≤65 mm Hg.[10 11] We are using a modified qSOFA score to maximise both clinical

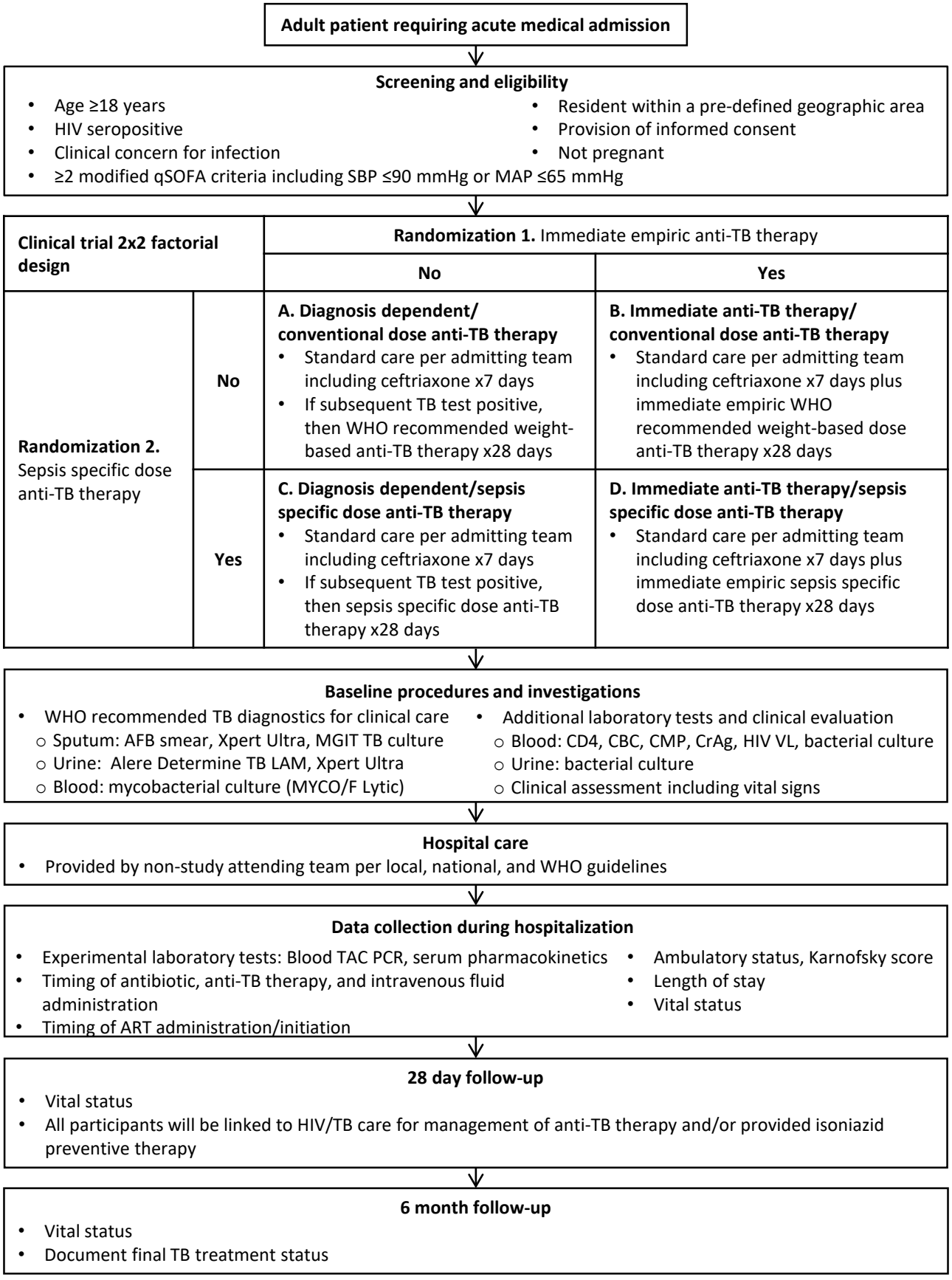

Figure 2 Schema of the ATLAS trial. ART, antiretroviral therapy; ATLAS, A randomised clinical TriaL of early empiric Anti-Mycobacterium tuberculosis therapy for Sepsis in sub-Saharan Africa; MAP, mean arterial pressure; SBP, systolic blood pressure; TAC, TaqMan Array Card.

simplicity as part of this pragmatic trial and to select participants who are at the highest risk of death and therefore the most likely to benefit from early empirical anti-TB therapy.[7 10 12 13] Study participants found to have a positive serum cryptococcal antigen test will be excluded as they would have a high expected case fatality rate and among those receiving anti-TB therapy would bias the study outcome to a null result whether or not they also had TB.[14] We will also exclude potential participants with known active TB or who have received TB treatment in the 6 months preceding the time of presentation to the hospital (including isoniazid preventive therapy), pregnant or lactating women, and those with known liver disease or significant alcohol use.

Interventions

After participants have been screened and consented to join the study, they will be randomised by a computer-generated, permuted-block randomisation algorithm with random block sizes of 4 and 8 in a 1:1:1:1 ratio stratified according to site and the presence or absence of altered mental status at the time that informed consent was obtained. Randomisation and data capture and storage will be conducted via research electronic data capture (REDCap) software. The two treatment randomizations include (1) immediate initiation of anti-TB therapy plus standard care or diagnosis-dependent anti-TB therapy plus standard care, and (2) sepsis-specific dosed anti-TB therapy with rifampin (~30 mg/kg), isoniazid (~7.5 mg/kg), pyrazinamide, and ethambutol using a combination of single dose (isoniazid and rifampin) and fixed dose combination tablets, plus pyridoxine or conventional WHO recommended weight-based anti-TB therapy with rifampin (~10 mg/kg), isoniazid (~5 mg/kg), pyrazinamide, and ethambutol in fixed dose combination tablets, plus pyridoxine, as recommended by WHO's 'Treatment of Tuberculosis Guidelines' and the Uganda and Tanzania Ministries of Health.[15] All participants receive serial blood testing to monitor for adverse events possibly associated with study interventions (table 1).

Participants not randomised to immediate initiation of anti-TB therapy but who are subsequently found to have TB by WHO-recommended TB tests (sputum and urine Xpert MTB/RIF Ultra, Alere Determine LF-Lipoarabinomannan (LAM) and/or TB culture) or clinically diagnosed with TB will receive anti-TB therapy with the dosing to follow the 'Randomization 2' assignment (figure 2). Hence, the 2×2 factorial design will create four distinct study groups: (1) immediate empirically initiated conventional anti-TB dose treatment, (2) immediate empirically initiated sepsis-specific anti-TB dose treatment, (3) diagnosis-dependent conventional anti-TB dose (only administered if ultimately confirmed or clinically suspected to have TB), and (4) diagnosis-dependent sepsis-specific anti-TB dose (only administered if ultimately confirmed or clinically suspected to have TB). According to the WHO Integrated Management of Adolescent/Adult Illness Guidelines for severe infections, ceftriaxone is the first-line recommended agent for the treatment of bacterial sepsis, as it treats the most common non-TB bacterial pathogens.[16] Thus, all study participants will be administered ceftriaxone for 7 days, but clinicians may alter this portion of the treatment regimen as needed based on the clinical scenario.

Participants receiving anti-TB therapy (conventional or sepsis-specific dose) will receive anti-TB therapy per protocol until 28 days to coincide with the evaluation

Table 1 Schedule of events for the ATLAS trial

Data collection instrument	Screening/ enrolment Day 1	Day 2	Day 3	Day 7	Day 14	Day 21	Day 28	Discharge	6 Months	Unscheduled visit
Screening	•									
Verification of consent	•									
Randomisation	•									
Baseline chart review	•									
Vital signs	•	•	•	•	•	•	•	•	•	•
Baseline medical assessment	•									
Concomitant medication review	•	•	•	•	•	•	•	•	•	•
Baseline specimen collection	•	•								
Study drug medications follow-up		•	•	•	•	•	•	•	•	•
Follow-up outcomes		•	•	•	•	•	•	•		•
Follow-up specimen collection				•	•	•	•			•
6 month follow-up									•	
PK sampling			•							

ATLAS, A randomised clinical TriaL of early empiric Anti-Mycobacterium tuberculosis therapy for Sepsis in sub-Saharan Africa; PK, pharmacokinetic.

of the primary endpoint of 28-day mortality, which is a frequently used endpoint for sepsis trials and allows for close follow-up in our study settings.[17] Study personnel will be responsible for linkage of all participants and their TB test results to the local antiretroviral/TB clinic where their care will be managed from 28 days forward. We anticipate that the overwhelming majority of study participants who receive TB treatment and survive to the 28-day evaluation will be continued on conventional TB treatment but stakeholders in Tanzania and Uganda preferred this decision to be made independent of the study team. Study participants randomised to sepsis-specific anti-TB therapy dosing who continue on anti-TB therapy after 28 days will revert to conventional WHO recommended weight-based dosing. Participants not randomised to empiric immediate initiation anti-TB therapy who do not subsequently receive anti-TB therapy will be linked to care for consideration of isoniazid preventive therapy at 28 days.

Diagnostic testing, procedures and definitions

The trial was open for enrollment on 4 June 2021. The duration of the trial is expected to last 36 months. Study procedures start at screening and continue through 6 months of follow-up (table 1). Data will be entered into a REDCap software database. Study personnel at each site will complete informed consent forms, case report forms, and data collection tools according to standard operating procedures and as determined by regulatory authorities. All study documents will be stored securely at the study sites for a minimum of 5 years. If a protocol change is required, it will be submitted to the relevant ethics committees for approval.

At enrolment, all participants will undergo sampling of blood, sputum, and urine to identify the aetiology of sepsis through conventional microbiological methods and novel assays and for future biomarker studies. Conventional methods will include culture of blood (BacTec 9050), sputum, and urine for bacteria. For evaluation of TB, all participants will have WHO-approved rapid TB diagnostics including GeneXpert MTB/RIF Ultra on sputum and urine, Alere Determine LF-LAM on urine, as well as mycobacterial culture of sputum (MGIT 960 system) and blood (BACTEC Myco/F system). Serum cryptococcal antigen will be tested on blood from all potential participants prior to enrollment. Rapid malaria testing and other targeted pathogen testing will be at the discretion of the treating clinician. Novel diagnostics will include the use of the multiplex TaqMan Array Card (TAC) assay which targets 44 pathogens associated with febrile illness in East Africa, to be run in batch analysis[5] (figure 3). The final aetiology of sepsis will be defined as 'confirmed TB sepsis' if any of the rapid diagnostic tests (Xpert MTB/RIF Ultra, Alere Determine LF-LAM, sputum AFB smear) are positive, or if *M. tuberculosis* complex is identified by mycobacterial culture or TAC assay; 'non-TB sepsis' if the bacterial cultures or TAC assay identify a causative pathogen (excluding cytomegalovirus or *Plasmodium* species monoinfection by TAC card, as these may be co-occurring infections that are not primary drivers of sepsis in adults); and 'unconfirmed sepsis' if all diagnostic assays are negative.[5 18]

Data analysis plan

The survival time for each participant will be defined as the time from randomisation until death, discharge (alive) prior to 28 days, or censored (alive) at day 28. Kaplan-Meier curves will be used to estimate the survival distribution. Comparisons at day 28 will be based on survival estimates and standard errors after complementary log–log transformation. Subsequent confirmatory analyses will use Cox proportional hazards models to estimate the main effects of timing and dose, adjusting for the stratification factors (site and altered mental status) and whether or not the participant tested positive for TB. A second proportional hazards model will also be fitted, which will estimate main effects of timing and dose and add participant characteristics at baseline to the previous model. While the analyses are focused primarily on the main effects, subsequent exploratory analyses will estimate and test for interactions between timing and dose.

For in-hospital mortality, we anticipate no censoring and X^2 tests will be used to compare the randomised treatment groups. Subsequent analyses will use logistic regression to compare in-hospital mortality among the randomised treatment groups, adjusting for participant characteristics. For 6-month mortality, we anticipate that many observations will be censored prior to 6 months, that is, participants are known to be alive at a point prior to 6 months but are lost to follow-up prior to the 6 month visit. The analyses for this endpoint will be the same as for the primary 28-day mortality, in which we will estimate and compare the survival curves among the groups at a specific point in time (6 months). For other 'time-to-event' endpoints, including duration of hospitalisation, time to ambulation, time to temperature normalisation, and time to anti-TB therapy (within the diagnosis-dependent groups), the substantial level of mortality requires that mortality be taken into account in comparing the time-to-events distributions among groups.[19]

For comparing adverse events, the proportion of participants experiencing at least one adverse drug event will be tabulated and compared with a X^2 test. Subsequent analyses will use logistic regression to compare the proportions adjusting for clinical and laboratory variables. X^2 tests will also be used to compare the groups with respect to the final sepsis aetiology. Methods for ordinal categorical variables, such as the proportional models, will be used to compare the groups with respect to Karnofsky score. The assumptions underlying this model will be checked and if the proportional odds assumption does not hold, continuation ratio models will be used. Subsequent analyses will add clinical and laboratory variables to compare the groups after adjusting for these variables.

For the analysis of the subset of participants undergoing PK testing, we hypothesise that sepsis-specific

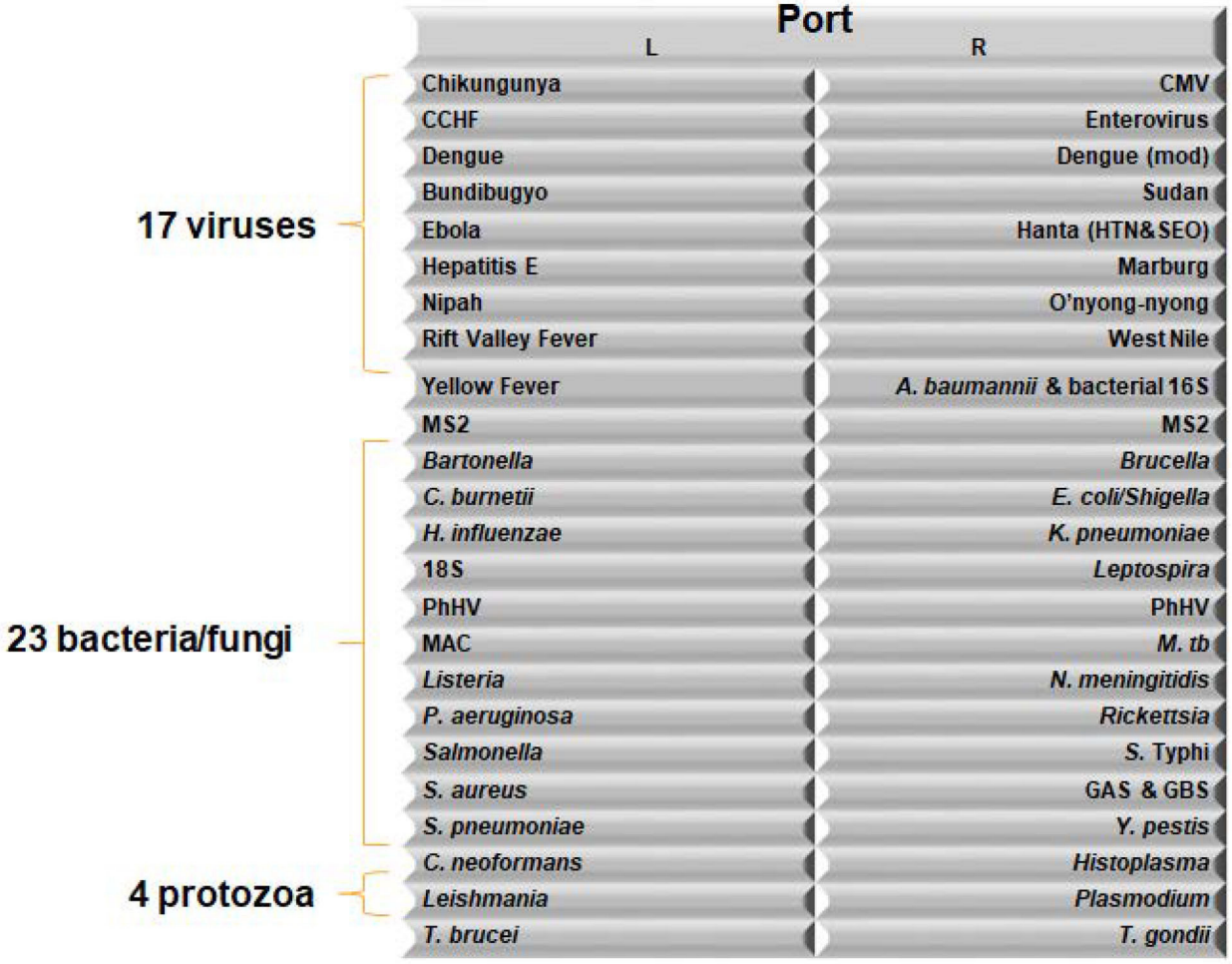

Figure 3 Example of a quantitative PCR-based TaqMan Array Card used to determine aetiology of bloodstream infection in the ATLAS trial. ATLAS, A randomised clinical TriaL of early empiric Anti-Mycobacterium tuberculosis therapy for Sepsis in sub-Saharan Africa.

dose anti-TB therapy will significantly increase serum concentrations of isoniazid in the early treatment interval compared with conventional dosing, and >95% of participants treated with sepsis specific dosing for rifampin will have Cmax and AUC at or above target values. Furthermore, those with confirmed TB sepsis and PK parameters within target range are expected to have a significantly faster time to clinical improvement. We will select those participants randomised to immediate anti-TB initiation to have timed blood sampling on day-2 after treatment and perform PK testing on all (n=218). We will collect four venous blood draws within the dosing interval (1, 2, 4 and 6 hours after medication administration). Serum will be stored at −80°C and serum concentrations will be measured using validated high-performance liquid chromatography for isoniazid and liquid chromatography–tandem mass spectrometry for rifampin.

The PK exposure-clinical outcome relationship will be evaluated based on the final aetiology of sepsis by comparing Cmax, Tmax, clearance (CL/F) and AUC to markers of early clinical recovery. Isoniazid and rifampin PK parameters will serve as exposure variables. Early assessments of clinical improvement are the outcome measures as continuous-valued variables, including time to durable normalisation of temperature,[20] time to ambulation,[21] Karnofsky score,[11] length of hospitalisation, and time to death, stratified by final aetiology of sepsis categorization. These endpoints will be compared with general linear models or Wilcoxon rank-sum tests, as appropriate. Death will be considered a competing risk.

Overall trial safety and planned interim analyses

The number and type of adverse events will be tabulated by treatment group and site. χ^2 tests will be used to compare the groups on the proportion of patients in each group experiencing severe adverse events. Analyses are planned for after 25%, 50%, 75% and 100% of participants have reached the primary endpoint determination. The interim analyses will be guided by Lan-Demets boundaries using the O'Brien Fleming spending function for efficacy and futility.[22] The boundaries will be applied separately to the main effects of timing and dose. The study Data Safety Monitoring Board (DSMB) will have the responsibility for recommending changes to the study

based on these interim analyses. These decisions could include terminating the study based on safety concerns, or terminating accrual to one or more of the anti-TB therapy groups. In the case that accrual to at least one group is terminated, the DSMB, with the assistance of the study statistician, will make a recommendation as to how remaining participants should be allocated.

Sample size calculation

Sample size calculations indicate that enrolling 109 participants per group (a total of 436 participants) yields sufficient power to meet the primary objectives of the trial, to examine the main effects of the timing of anti-TB therapy and the use of sepsis-specific dosing on 28-day mortality. To reach this goal, each of two regional sites in Moshi, Tanzania and Mbarara, Uganda will enrol 218 participants over a 3-year period, a requirement of 72–73 participants per country per year. This calculation allows for 20% of participants to be discharged (alive) prior to day 28. Kaplan-Meier curves will be used to estimate the survival distribution for each of the four groups, estimating and comparing 28-day mortality based on the complementary log-log transformation.[23]

The sample size was calculated to give 80% power, with a two-sided significance level of 5%, for testing each of the main effects of timing and dose on 28-day mortality, assuming a 28-day mortality of 45% in the diagnosis-dependent timing/conventional dose group (upper left cell 'a' in figure 2), 32% in each of the diagnosis-dependent timing/sepsis-specific dosing and immediate timing/conventional dose groups (off-diagonal cells 'b' and 'c' in the figure 2), and 19% in the immediate timing, sepsis-specific dose group (lower right cell 'd' in the figure 2). The calculations allow for a 20% loss to follow-up. An interaction plot for these assumed proportions is shown in figure 4.

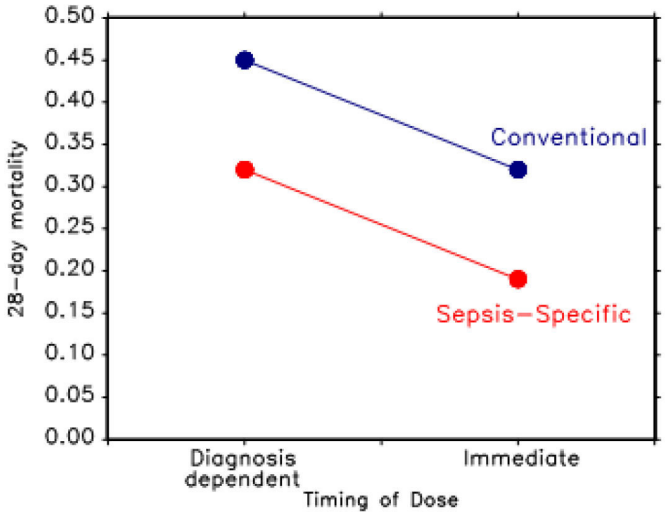

Figure 4 Interaction plot of estimated effects of immediate and sepsis-specific dosing strategies in the ATLAS trial. ATLAS, A randomised clinical TriaL of early empiric Anti-Mycobacterium tuberculosis therapy for Sepsis in sub-Saharan Africa.

Data availability

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, the ATLAS trial is registered at ClinicalTrials.gov; information and results from this trial will be submitted to ClinicalTrials.gov. In addition, we will publish results in peer-reviewed journals. Data from this study may be requested 5 years after the completion of the primary endpoint by contacting the principal investigators Moore and Heysell; however, a portion of data will be deposited in a publically accessible repository (eg, NIH TB Portals), as per NIH guidelines.

Patient and public involvement

As we prepared the trial protocol to submit for funding, we convened community advisory boards in both Tanzania and Uganda composed of lay stakeholders, religious leaders, and non-affiliated medical personnel to discuss the merits of the study to discuss the trial. The response from both Tanzanian and Ugandan community advisory boards was overwhelmingly supportive of the trial and for inclusion of the conventional dosing arm. The results of the study trial will be disseminated in the lay press, scientific conferences, and in peer-reviewed journals.

DISCUSSION

Here, we present the ATLAS trial, a 2×2 factorial randomised clinical trial which aims to determine whether immediate and/or sepsis-specific dosing will improve 28-day mortality for study participants admitted to hospital with HIV and sepsis in Tanzania and Uganda. In doing so, we will determine the optimal content, timing, and dosing of antimicrobial therapy for sepsis in areas with a high HIV and TB prevalence in sub-Saharan Africa.

The WHO endorses a stepwise empirical initiation of anti-TB therapy among patients who are unable to be tested for TB by sputum smear and/or urine LAM, or have been tested but have negative results. Specifically, seriously ill hospitalised patients in HIV-endemic settings with a history of prolonged cough should receive anti-TB therapy only if they have not demonstrated clinical improvement while receiving routine parenteral antibiotics for 3–5 days. In a study of 467 patients from Tanzania, this stepwise treatment algorithm led to missed treatment in 48% of patients who ultimately had TB positive sputum cultures.[24] These data suggest that additional survival benefit could be accrued from early anti-TB therapy.

There are other published clinical trials of empirical anti-TB therapy in participants with HIV. The REMEMBER study was a clinical trial of empirical combination anti-TB therapy for active TB disease compared with isoniazid preventative therapy in outpatients with advanced HIV initiating antiretroviral therapy (ART) that took place at 18 sites in 10 countries.[25] Patients identified with active

TB at screening were excluded. There was no difference in the primary outcome of death or unknown vital status 24 weeks after randomisation, which occurred in 5% of study participants. There was an increased rate of AIDS progression in the empirical anti-TB treatment group, mainly due to an increased incidence of TB. This finding was attributed to possibly increased discontinuation rates of ART and anti-TB therapy, diagnostic suspicion bias, and less likely unmasking TB-immune reconstitution inflammatory syndrome in the empirical anti-TB treatment group. Similarly, in the STATIS study conducted in six centres at two sites in Africa and two sites in Southeast Asia, there was no difference in death or invasive bacterial infection over 24 or 48 weeks among adults with advanced HIV who had not previously received ART who received systematic empirical anti-TB therapy when compared with those who received TB screening guided anti-TB therapy.[26] The overall mortality in this trial was 9%.

In these empirical anti-TB therapy trials in predominantly outpatients with HIV, the mortality was much lower than would be expected from a sepsis clinical trial where case fatality rates are expected to be 20%–50%. Furthermore, there is a higher likelihood of active disseminated TB in patients with HIV and sepsis compared with outpatients initiating ART. Therefore, the incremental benefit of empirical anti-TB therapy is likely to be higher in this ATLAS trial of anti-TB therapy for sepsis compared with prior studies of empirical anti-TB therapy in the outpatient setting. There are a myriad of non-TB infections that can lead to sepsis in this region including Enterobacteriaceae, non-Typhoid *Salmonella*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* among others.[5 27] It is also possible that there may be additional benefit of an anti-TB regimen that includes rifampin, in addition to the ceftriaxone that all study participants will receive, in the treatment of non-TB infections. We are further optimistic that our inclusion of a sepsis-specific dosing arm will provide additional discrimination of benefit among a patient population with a high likelihood of suboptimal exposure of anti-TB drugs when otherwise given at conventional doses.[9]

The ATLAS trial is anchored on early TB intervention and optimisation of the key anti-TB drugs, rifampin and isoniazid. The major potential limitation of the trial design is the lack of blinding, which could introduce bias based on known treatment allocation and potentially alter participant outcomes. However, it would be logistically challenging to mask immediate vs diagnosis-dependent anti-TB therapy, which could lead to allocation errors. Furthermore, given the high severity of illness of study participants, we expected a high case fatality rate which would require knowledge of the randomisation assignment and whether or not participants were receiving anti-TB therapy and at what dose. Another limitation of the trial is the potential for differences in clinical management of study participants at the two trial sites. To counter this limitation, the study teams, along with local clinicians, will oversee the management of the study participants and will adhere to the WHO guideline recommendations for the treatment of patients with HIV and suspected TB.[15] Nonetheless, at its conclusion, the results of the ATLAS trial will provide the optimal content, dosing and timing of antimicrobial therapy for sepsis in high HIV and TB prevalent settings, which will have significant implications for national and international sepsis treatment guidelines.

Ethics and dissemination

The study is funded by the National Institutes of Health in the US and will be performed according to the Declaration of Helsinki and Good Clinical Practice. The trial is registered at ClinicalTrials.gov (NCT04618198). Institutional review board approval was conferred by the University of Virginia (HSR200253), the Tanzania National Institute for Medical Research (NIMR/HQ/R.8a/Vol. IX/3664), and the Uganda National Council for Science and Technology (HS1272ES). Written informed consent will be obtained from each study participant (online supplemental file 1). Study results will be published in peer-reviewed journals and presented at international scientific conferences. We will also present our findings to our community advisory boards and aim to publish our findings in the lay press of Tanzania and Uganda.

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Contributors CCM, SKH, SGM, MC and CM conceptualised and designed the clinical trial with significant contributions from BS, EN, AL, DRB, MC and TT. MC led the statistical analysis plan. PB led the pharmacy plan. CCM and SKH secured funding for the clinical trial. RA created the REDCap database and randomisation procedures with MC. SM, AL, BS and MN led the implementation of the protocol in Tanzania with significant contributions from AC and CG. CM, EN, RM, and MN led the implementation of the protocol in Uganda with significant contributions from SJ and PT. All authors provided technical inputs in the proposal. SB, EN, CCM and SKH led the writing of the manuscript with contributions from all authors. All authors have approved the final version and agreed to be accountable for all aspects of the work related to accuracy and integrity. BS, EN, CCM, SKH, CM and SM are responsible for the overall content as guarantors.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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IRB HSR # _____ DMID # _____
A Randomized Clinical Trial of Early Empiric Anti-Mycobacterium Tuberculosis Therapy for Sepsis in Sub-Saharan Africa (ATLAS trial)

Participant's Name_____

INTERNATIONAL RESEARCH CONSENT FORM
--CONSENT TO PARTICIPATE IN A RESEARCH STUDY--

What is this study about?

This is a research study to find which medicines work better to treat sepsis caused by tuberculosis (TB). Sepsis is a serious infection in the blood. It can cause death when the body cannot fight the infection. Many people living with HIV in Uganda and Tanzania are carrying TB germs in their bodies but do not know it. The doctors think that immediately giving TB medicine to people living with HIV who are diagnosed with sepsis could improve their chances of surviving. Doctors at the Kibong'oto Infectious Diseases Hospital, Mbarara University of Science and Technology and the University of Virginia in the United States are trying to learn more about the best ways to treat sepsis.

Our team will compare results between four groups of participants who are admitted to the Mbarara Regional Referral Hospital in Mbarara, Uganda, or Kibong'oto Infectious Diseases Hospital in Kilimanjaro or affiliated hospitals in the Kilimanjaro region of Tanzania: (1) participants who receive regular sepsis medical care and standard dose of TB medicine if they are diagnosed with TB (drugs begin immediately after a diagnosis of TB is made), (2) participants who receive regular sepsis medical care, plus immediate anti-TB medicine at the standard dose (drugs begin immediately on the day you begin the study), (3) participants who receive regular sepsis medical care, plus a higher dose of TB medicine for research if they are diagnosed with TB, and (4) participants who receive regular sepsis medical care, plus immediate anti-TB medicine at a higher dose for research . If no diagnosis of TB is made, study participants will not receive TB medicine unless they are in one of the two groups that receive immediate TB medicine.

All groups receive regular sepsis care, plus you will be assigned to 1 of the 4 groups by a computer. If you join this study, you will not be able to pick which group you are in. If you do NOT join the study, you will receive medical care like Group 1.

- Group 1: Standard-dose of TB drugs begin after a TB diagnosis is made
- Group 2: Standard-dose of TB drugs begin immediately
- Group 3: High-dose of TB drugs begin after a TB diagnosis is made
- Group 4: High-dose of TB drugs begin immediately

IRB HSR # _____ DMID # _____
A Randomized Clinical Trial of Early Empiric Anti-Mycobacterium Tuberculosis Therapy for Sepsis in Sub-Saharan Africa (ATLAS trial)

The reason to do this research study is to find a better way to treat people living with HIV who are diagnosed with sepsis and to improve their chances of surviving, especially during the first week after being admitted to the hospital.

You are asked to be a participant in this research study because you are living with HIV and have been diagnosed with sepsis**.**

The researchers in charge of this study are Dr. Stellah Mpagama of Kibong'oto Infectious Disease Hospital in Kilimanjaro, Tanzania, Dr. Conrad Muzoora of Mbarara University of Science and Technology in Mbarara, Uganda, Dr. Christopher Moore of the University of Virginia (USA) and Dr. Scott Heysell of the University of Virginia (USA).

This study will take place at Mbarara Regional Referral Hospital and Kibong'oto Infectious Diseases Hospital as well as the affiliated hospitals in the Kilimanjaro region of Tanzania. If you participate in this study, you would be one of 436 participants and your involvement would last until you complete TB treatment (no longer than 6 months after study enrollment).

What will happen during the study?

If you agree to participate, we will have six in-person visits and monthly telephone follow-up calls until your TB treatment ends. Detailed information about these visits/follow-ups include:

#1 Enrollment study day 1: This will be a 2-night visit in the hospital. The minimum length of stay in the hospital will be the time required to complete research blood draws. Routine care is 2 days or longer for patients admitted with sepsis.
If you agree to participate, you will read and sign this consent form before any study procedures take place.

- You will get routine antibiotics for the treatment of sepsis.
- A computer will assign you to one of the four TB-treatment study groups:
  - Group 1: Standard-dose of TB drugs begin after a TB diagnosis is made
  - Group 2: Standard-dose of TB drugs begin immediately
  - Group 3: High-dose of TB drugs begin after a TB diagnosis is made
  - Group 4: High-dose of TB drugs begin immediately
- You will be asked some questions about current symptoms, past medical history and medications.
- We will document your vital signs, height and weight and perform a physical exam.
- You will have your blood drawn by a nurse/doctor

- This blood will be used to check your HIV status, blood counts, and test for other germs in your blood that can be making you sick. The tests will be performed at the hospital and a research laboratory nearby. Results will be given to you and your doctors.
- Any leftover blood or urine samples will be stored at the laboratory until the conclusion of the study. At the conclusion of the study, deidentified samples will be stored for their possible use in future studies. We will not perform any genetic tests on your blood samples.

- You will be asked to provide a urine sample.
  - The urine will be used to check for the *Mycobacterium tuberculosis*, the germ that causes tuberculosis (TB) and other germs that could be making you sick. (For female participants): A pregnancy test will be checked from the urine. If you are pregnant, you will not be eligible for the study.
  - Any leftover urine will be stored at the laboratory until the conclusion of the study.
- If you allow us to store your blood and urine samples, it means that you will be giving them to us for testing and for research. The samples will be under the responsibility of the researchers listed below. They may be shared with other researchers to assist with testing. They will not be sold. Some of the storage and testing of your samples for research will happen locally in Tanzania or Uganda, and some will happen in the United States. The samples will be stored forever, unless you tell us to destroy them.
- You will be asked to provide a sputum sample.
  - The sputum will be used to check for the *Mycobacterium tuberculosis*, the germ that causes tuberculosis (TB).
  - The tests will be performed at the hospital. Results will be given to you and your doctors.
- If the blood tests show that you are not HIV-positive, or if you have an allergy to TB medicines or other medicines that interact with the study drugs, you will not be able to participate in the study, but you will be referred to a doctor at this hospital for any additional medical care.
- You will receive the first round of 28 days' worth of sepsis treatment, according to the study group that you were randomly assigned, at no cost to you.

<u>#2 Enrollment study day 2:</u> (if you are on TB treatment)

1. You will have your blood drawn by a nurse/doctor at four (4) timed intervals (hour-1, 2, 6, 12) after you take your anti-TB medication. This blood will be used to check the amount to anti-TB medication that is in your blood. These tests will be performed in a specialized research laboratory.

IRB HSR # _____ DMID # _____
A Randomized Clinical Trial of Early Empiric Anti-Mycobacterium Tuberculosis Therapy for Sepsis in Sub-Saharan Africa (ATLAS trial)

#3 In-person follow-up visits (1 week, 2 weeks and 3 weeks into TB therapy)

1. You will be asked some questions, including any current symptoms and medications.
2. We will document your vital signs, height and weight and perform a physical exam.
3. You will be asked to provide a blood sample. The blood may be used to measure the levels of the TB drugs in the body and your blood counts, liver function and kidney function. The tests will be performed in the hospital and the research laboratory.

#4 Final follow-up phone call (no longer than 6 months into TB treatment)

1. We will communicate with you via telephone to ask you some questions about your health.

Could the research hurt me?

Sometimes things happen to people in research studies that may hurt them or make them feel bad. These are called risks. The risks of participating in this study include:

1. Medications given in this study may cause side effects. Participants who are randomly assigned to receive standard or sepsis-specific TB medicine may experience the following common symptoms including, but not limited to nausea, vomiting, abdominal pain, and nerve damage that causes a loss of sensation or movement in part of the body. A less likely, yet more serious side effect includes liver damage. Doctors will monitor all patients' liver health regularly and will provide treatment for any symptoms as needed, including taking away the study drug, if necessary.
2. Pain or discomfort from the needle stick used for blood draws. Sometimes this can lead to bruising. Very rarely, an infection can develop where the blood is taken. This is no different than routine medical care. In order to minimize the chances of these risks, only experienced nurses and/or doctors will be asked to do this procedure.
3. Loss of confidentiality: We will take great care to protect your information by using it only for our research purposes. Only a part of the research team will have access to information such as your name; this information will be kept in a locked and secure location and will not be released to others outside the team.

(For female participants) If you are pregnant or think you might be pregnant, please tell us so we can talk about this with you.

Could the research help me?

People also might have good things happen to them because they are in research studies. These are called benefits. The benefits to you of being in this study might be:

IRB HSR # _____ DMID # _____
A Randomized Clinical Trial of Early Empiric Anti-Mycobacterium Tuberculosis Therapy for Sepsis in Sub-Saharan Africa (ATLAS trial)

1. Getting additional test results such as the blood counts and urine results.
2. Additional medical attention that you receive from the research team (nurse/doctor), including additional education about the nature of sepsis, HIV and/or TB disease and how it impacts you and your family.
3. Participants who receive TB medicine may have improved health outcomes at the 28 days and 6 month marks. All participants are likely to have urine- and sputum-based TB tests performed more quickly than people who do not participate in the study.
4. The study could help doctors in other areas of the country (and around the world) where HIV and TB are widespread, to learn how to better treat patients who have sepsis and improve their chances of surviving the disease.

The doctor and/or the researcher will inform you of any relevant information found from the conduct of this study that is important to your personal medical care or situation.

How will my privacy be protected?

Study records that identify you will be kept confidential as required by the regulatory authorities in Tanzania, Uganda and the United States. If you sign this consent, you agree to allow the researchers to use and disclose health information about you to conduct this study. If required by the National Institutes of Health (NIH), these individuals or their designees may also release your medical records, the consent form associated with this study, this authorization and the information about you created by this study to NIH or their designates. In addition, the information created about you may be shared with other institutions doing this study. Other persons who may have access to your records include groups such as data and safety monitoring boards which oversee the safety of a study including accrediting agencies, or Tanzania, Uganda and United States federal, state and local agencies having oversight over this research.

The researchers leading this study include Dr. Stellah Mpagama, Dr. Conrad Muzoora, Dr. Tania Thomas, Dr. David Boulware, Dr. Christopher Moore, Dr. Scott Heysell and their staff (researchers associated with their staff and Kibong'oto Infectious Disease Hospital, Mbarara University of Science and Technology, the University of Minnesota and the University of Virginia).

If you sign this form, you have given us permission to release information to these other people. There is no expiration date to this permission. If you decided to withdraw your permission and end this agreement to release the information collected about you, please contact Dr. Stellah Mpagama, Kibong'oto Infectious Diseases Hospital, Mae Street, Lomakaa

IRB HSR # _____ DMID # _____
A Randomized Clinical Trial of Early Empiric Anti-Mycobacterium Tuberculosis Therapy for Sepsis in Sub-Saharan Africa (ATLAS trial)

Road. Siha – Kilimanjaro, Tanzania (phone number: +255 272 97141), or Dr. Conrad Muzoora, Mbarara University of Science and Technology, Mbarara, Uganda (phone number: +256 772 547175). They will help you document in writing your decision to withdraw this permission. Please note that any information already obtained will continue to be used.

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. There is potential that information released to the NIH or governmental agencies may be released again and would no longer be protected by privacy laws.

Your participation in this research study is voluntary. However, you will not be allowed to participate in this research if you do not sign this form.

Will I be compensated for my participation?

We will provide travel reimbursement and meals for the follow-up visits. Study participants who complete the week 28 visit will be compensated with one year's worth of health insurance.

Do I have to participate?

You do not have to be in this study if you do not want to. This means your participation is voluntary. It is up to you to decide whether or not being in the study is in your best interest.

You can also stop participating in this study at any time. Any information gathered about you before you decide to stop this study will continue to be used. If you decide to stop, no one will be angry or upset with you. No one will treat you differently if you decide not to be in this study. Any new findings that develop during the course of the study which may impact your willingness to continue in the study will be shared with you. Your participation in the research may be stopped by the study team without your consent if your continued participation in the study is not thought to be in your best interest.

If I don't want to participate, what other choices do I have?

The only alternative is to not participate in this study**. You will still receive all the medical care necessary to manage your sepsis.**

Who can I contact with questions about my rights as a research subject?

Uganda National Council for Science and Technology
P.O. Box 6884
Plot 6, Kimera Road, Ntinda
Kampala, Uganda

Telephone +256 414 705500)

National Health Research Ethics Review Committee
National Institute for Medical Research
2448 Ocean Road
P.O. Box 9653, Dar es Salaam, Tanzania
Tel: +255 22 2121400
Fax: 255 22 2121360
Website: www.nimr.or.tz

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908 USA
434-924-2620
irbhsr@virginia.edu

Who can I contact with questions about this study?

Dr. Stellah Mpagama, Kibong'oto Infectious Diseases Hospital, Mae Street, Lomakaa Road. Siha – Kilimanjaro, Tanzania, +25527297141 (tel), +255754860576 (mobile), sempagama@yahoo.com or sempagama (Skype)

Dr. Conrad Muzoora, Mbarara University of Science and Technology, Mbarara, Uganda, +256 772 547175 (mobile), conradmuzoora@gmail.com (email) or conrad.muzoora (Skype)

Dr. Christopher Moore, University of Virginia, PO Box 801340, Charlottesville, Virginia, USA 22908-1340, +1-434-924-9678 (office) or ccm5u@virginia.edu

Dr. Scott Heysell, University of Virginia, PO Box 801340, Charlottesville, Virginia, USA 22908-1340, +1-434-243-9064 (office) or skh8r@virginia.edu

IRB HSR # _____ DMID # _____
A Randomized Clinical Trial of Early Empiric Anti-Mycobacterium Tuberculosis Therapy for Sepsis in Sub-Saharan Africa (ATLAS trial)

Signatures

Please ask as many questions as you need to make sure you understand the study before you sign this form.

_____	_____	_____
PARTICIPANT'S NAME (SIGNATURE OR THUMB PRINT)	PARTICIPANT'S NAME (PRINT)	DATE

_____	_____	_____
SURROGATE CONSENTER'S NAME (SIGNATURE)	SURROGATE CONSENTER'S NAME (PRINT)	DATE

_____
(RELATIONSHIP TO PARTICIPANT)

If the potential participant is unable to sign and date the informed consent form but has delegated decision-making authority to a surrogate consenter, the surrogate must sign and date the lines above and indicate their relationship to the potential participant. Otherwise, leave these lines blank.

_____	_____	_____
INTERPRETER'S NAME (SIGNATURE)	INTERPRETER'S NAME (PRINT)	DATE

If an interpreter was used to explain this study to a potential participant, then the interpreter must sign and date the lines above. Otherwise, leave these lines blank.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE