# Immediate or high-dose antituberculosis therapy for HIV-related sepsis in Tanzania and Uganda (ATLAS): a phase 3, open-label, randomised, controlled, 2 × 2 factorial, superiority trial

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## Summary

**Background** People living with HIV and hospitalised with sepsis in Africa are at risk of death due to tuberculosis but diagnostics for tuberculosis might be delayed or inaccessible for people presenting for critical care. We aimed to compare the effects of immediate empirical and high-dose antituberculosis therapy on 28-day mortality in adult people living with HIV with sepsis in east Africa.

**Methods** ATLAS was a phase 3, open-label, randomised, controlled, 2×2 factorial, superiority trial conducted at four hospitals in Tanzania and Uganda. Participants were aged 18 years or older, living with HIV, and had been admitted to hospital with sepsis with two or more modified quick Sequential Organ Failure Assessment score criteria. Exclusion criteria were active tuberculosis or receipt of antituberculosis therapy within 6 months of hospitalisation, pregnancy or lactation, allergies to antituberculosis therapy, another investigational drug within the past month, chronic liver disease, heavy alcohol use, positive serum cryptococcal antigen, or anticipated significant drug–drug interaction with rifampicin. A computer-generated permuted-block algorithm with allocation concealment and random block sizes of four and eight randomly assigned participants (1:1) to receive either immediate or diagnosis-dependent antituberculosis therapy, and (1:1) to receive either high-dose or conventional WHO-recommended weight-based dose antituberculosis therapy. Allocation was stratified by country and the presence of altered mental status at the time of randomisation. Participants randomly assigned to conventional-dose antituberculosis therapy received fixed-dose combination tablets of rifampicin approximately 10 mg/kg, isoniazid approximately 5 mg/kg, pyrazinamide, and ethambutol, plus pyridoxine 50 mg orally. Participants randomly assigned to receive high-dose antituberculosis therapy received rifampicin approximately 30 mg/kg and isoniazid approximately 7·5 mg/kg as a combination of single formulation tablets and fixed-dose combination tablets that included WHO-recommended weight-based doses of pyrazinamide and ethambutol, plus pyridoxine. Participants continued immediate antituberculosis therapy for 28 days. All medications were administered daily. Participants in the diagnosis-dependent antituberculosis therapy groups received treatment based on a clinical or microbiological diagnosis of tuberculosis. All participants received 2 g intravenous ceftriaxone daily for 7 days. The primary endpoint was 28-day mortality analysed in the modified intention-to-treat population and in the subgroup with later confirmed tuberculosis. We defined the survival time for each participant as the time from randomisation until death, discharged (alive) by day 28, or censored (alive) at day 28. We graded adverse events according to recommendations from the National Institutes of Health Division of AIDS. This study was registered with ClinicalTrials.gov, NCT04618198, and is completed.

**Findings** Between Jan 5, 2022, and Dec 9, 2024, 707 people were screened for eligibility and 437 were randomly assigned (110 to immediate conventional-dose, 112 to immediate high-dose, 107 to diagnosis-dependent conventional-dose, and 108 to diagnosis-dependent high-dose antituberculosis therapy). 395 patients (226 [57%] of whom were female and 169 [43%] were male; all participants were Black) received study intervention and were analysed for the primary outcome of 28-day mortality. We confirmed tuberculosis in 204 (52%) patients. There was no evidence of differences in 28-day mortality in immediate antituberculosis therapy groups (50 deaths [25%] in 198 patients) compared with diagnosis-dependent groups (50 deaths [25%] in 197 patients; adjusted hazard ratio [aHR] 0·99 [95% CI 0·67–1·46]; p=0·95), or in high-dose antituberculosis therapy groups (51 deaths [26%] in 199 patients) compared with conventional-dose groups (49 deaths [25%] in 196 patients; aHR 1·07 [0·72–1·59]; p=0·73). In patients with microbiologically confirmed tuberculosis, the 28-day mortality relative to the diagnosis-dependent conventional-dose group (18 deaths [34%] in 53 patients) was lower for the immediate conventional-dose group (six deaths [12%] in 51 participants; aHR 0·32 [95% CI 0·13–0·82]; p=0·015); for the diagnosis-dependent high-dose group (11 deaths [20%] in 56 patients) was 0·51 (0·24–1·08; p=0·79); and for the immediate high-dose group (11 deaths [26%] in 43 patients) was 0·63 (0·29–1·36; p=0·24). No significant differences in adverse events occurred between treatment

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groups but numerically more events of drug-induced liver injury occurred in the immediate high-dose group compared with any other group.

**Interpretation** Among all participants with HIV-related sepsis, 28-day mortality was not significantly reduced with immediate or high-dose antituberculosis therapy. In the subgroup with later confirmed tuberculosis, immediate conventional-dose antituberculosis therapy significantly reduced 28-day mortality, suggesting, as in other forms of bacterial sepsis, that hours to active treatment might determine survival.

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## Introduction

Sepsis occurs due to life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] There are an estimated 48 million cases of sepsis annually, which lead to 11 million deaths.[2] Africa bears the highest burden of sepsis globally, with the greatest risk of mortality occurring among people living with HIV.[2] Tuberculosis accounts for an estimated 25–30% of sepsis cases in Africa, with an associated case-fatality rate of 30–50%.[3–6] The only randomised trials of adult sepsis management conducted in Africa include two negative studies of fluid resuscitation from Zambia.[5,6]

WHO recommends immediate antibacterial therapy for people living with HIV with clinical danger signs; however, antituberculosis therapy is recommended only for those with diagnosed tuberculosis or after 3–5 days of standard antibacterial therapy without clinical recovery.[7] Rapid tuberculosis testing, including urine lipoarabinomannan antigen (tested using lateral flow-lipoarabinomannan [LF-LAM]) and sputum Xpert MTB/RIF, is recommended

### Research in context

#### Evidence before this study

The highest incidence of sepsis and associated mortality occurs in Africa, particularly in areas of high HIV and tuberculosis prevalence. Yet, to our knowledge, there are only two previously published randomised clinical trials of adult sepsis therapy that were conducted in Africa. Both trials evaluated a fluid resuscitation strategy in Zambia and had negative outcomes. The leading cause of sepsis in people living with HIV in Africa is tuberculosis. Based on trials that showed decreased mortality with early tuberculosis testing, current WHO guidelines for people living with HIV with clinical danger signs recommend early rapid diagnostic testing for tuberculosis, including urinary lipoarabinomannan and sputum GeneXpert. The guidelines also recommend initial standard antibacterial therapy with antituberculosis therapy only for patients with a positive tuberculosis test result or after 3–5 days without clinical recovery. However, a substantial proportion of deaths due to tuberculosis-related sepsis in people living with HIV occurs during this 3–5-day period. We searched PubMed for English language literature related to empirical antituberculosis therapy from Jan 1, 2000, to June 30, 2025, with the following search terms: "tuberculosis", "therapy", "empiric or empirical", and "HIV". Several outpatient trials of empirical antituberculosis therapy conducted in Africa, south Asia, and South America, including the STATIS and REMEMBER trials, showed no reduction in mortality compared with targeted tuberculosis diagnostic testing or isoniazid preventive therapy in adults with advanced HIV disease starting antiretroviral therapy. However, there are no published trials of empirical antituberculosis therapy for patients hospitalised with critical illness due to sepsis in whom the timing of initiation of active antimicrobial therapy is of paramount importance for successful outcomes. Accordingly, the question of whether immediate empirical antituberculosis therapy reduces mortality in critically ill patients with sepsis remains unanswered. Similarly, the optimal dose of antituberculosis therapy for patients with critical illness is not known. There is growing evidence that pharmacokinetics–pharmacodynamics might be one of the most important drivers of tuberculosis treatment response, as suboptimal serum drug concentrations have been associated with worse outcomes for ambulatory patients with pulmonary tuberculosis. In a study of people living with HIV who were treated for pulmonary tuberculosis in Uganda, the time to microbiological clearance from the sputum was longer in people with isoniazid and rifampicin drug concentrations that were below expected peak serum concentrations. Furthermore, in a study of people living with HIV and sepsis, the majority had serum pharmacokinetics below the expected ranges for peak concentrations and total area under the concentration curve, the key pharmacokinetic determinants of microbial kill and prevention of acquired drug resistance, for rifampicin, isoniazid, or both. Two randomised trials among people with disseminated tuberculosis (NewStrat-TB) and tuberculosis meningitis (HARVEST) tested novel regimens including high-dose oral rifampicin but have reported results with either no benefit or harm. Thus, determination of the optimal timing and dose of antituberculosis therapy for people living with HIV and sepsis without an initial diagnosis of tuberculosis is urgently needed.

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**Added value of this study**

The ATLAS trial was the first randomised controlled trial to evaluate an antimicrobial strategy for people with HIV and sepsis in Africa. This trial advances the existing literature by providing the first randomised evidence to guide empirical antimicrobial management for sepsis in people living with HIV in Africa, a population with the highest global burden of tuberculosis-associated sepsis but minimal trial data. Unlike previous observational studies, ATLAS showed that tuberculosis is the predominant and often occult cause of sepsis in this patient population, often only detectable by blood-based assays. Although there was no overall benefit from immediate or high-dose antituberculosis therapy, there was an interaction between timing and dosing of antituberculosis therapy, such that the lowest 28-day mortality occurred in those receiving immediate conventional-dose antituberculosis therapy, with a number needed to treat to prevent one death of 17·2. In a planned subgroup analysis of those with ultimately confirmed tuberculosis, there was a significant reduction of mortality for those receiving immediate conventional-dose antituberculosis therapy compared with those who received the standard of care of diagnosis-dependent conventional-dose antituberculosis therapy. The number needed to treat with immediate conventional-dose antituberculosis therapy compared with the standard of care to prevent one death was only 4·4. Similar findings were noted from participants with tuberculosis bloodstream infection who received immediate antituberculosis therapy. Therefore, the ATLAS trial provides a new pragmatic, evidence-based treatment approach for sepsis in similar high HIV and tuberculosis burden settings in Africa.

**Implications of all the available evidence**

The standard of care antimicrobial regimen for sepsis in most of Africa is a third-generation cephalosporin based on commonly encountered non-tuberculosis bacterial pathogens causing bloodstream infection, and antituberculosis therapy is often started only after a diagnosis of tuberculosis is made. Immediate high-dose antituberculosis therapy did not improve mortality, a finding in line with other recent trials in people with confirmed disseminated tuberculosis including meningitis, and it is unknown if the lack of improvement was due to a deleteriously robust inflammatory response or precipitation of adrenal insufficiency. The significant improvement of mortality among those with ultimately confirmed tuberculosis and treated with immediate conventional-dose therapy occurred despite only small improvements in the time to tuberculosis treatment measured in hours. Thus, the apparent benefit of targeted therapy for tuberculosis sepsis might occur early, and as with other causes of bacterial sepsis, delays of hours of treatment might affect mortality. Conventional-dose antituberculosis treatment in a critically ill population did not prompt safety concerns, but a non-significantly higher number of drug-induced liver injuries occurred in the group receiving immediate high-dose antituberculosis treatment, a trend similar to reports of other high-dose rifampicin studies in people with disseminated tuberculosis. The ATLAS trial findings reinforce the importance of developing novel and highly sensitive diagnostics for the full spectrum of tuberculosis disease including sepsis. Until then and given the wide availability of oral antituberculosis medications, the intervention of immediate conventional-dose antituberculosis treatment represents an area of operational research priority applicable for high burden HIV and tuberculosis settings.

by WHO to diagnose tuberculosis in acutely ill people living with HIV, but it is often unavailable or delayed.[8] Accordingly, antituberculosis therapy is often deferred or not initiated in people living with HIV with sepsis. Moreover, conventional WHO-recommended doses of antituberculosis therapy often do not achieve expected therapeutic concentrations in adults with sepsis.[9] We aimed to compare the effects of immediate empirical and high-dose antituberculosis therapy on 28-day mortality in adult people living with HIV with sepsis in east Africa.

## Methods

### Study design and participants

A Randomized Clinical Trial of Early Empiric Antituberculosis Therapy for Sepsis in Africa (ATLAS) was a phase 3, multisite, open-label, randomised, controlled, 2×2 factorial, superiority trial of immediate initiation and high-dose antituberculosis therapy for people living with HIV with sepsis conducted at four hospitals in Tanzania and Uganda.[10] Local community advisory boards provided feedback on the trial protocol.

Participants were aged 18 years or older, living with HIV, and had been admitted to hospital with sepsis at Sekou Toure Regional Referral Hospital, Mwanza, Tanzania; Kibong'oto Infectious Disease Hospital, Kilimanjaro Region, Tanzania; Mbarara Regional Referral Hospital, Mbarara, Uganda; or Fort Portal Regional Referral Hospital, Fort Portal, Uganda. Sites were selected through existing clinical trials partnerships and each site served both rural and urban populations living with HIV. Participant eligibility criteria included concern for infection and two or more modified quick Sequential Organ Failure Assessment (modified qSOFA) score criteria, including systolic blood pressure 90 mm Hg or less or mean arterial pressure 65 mm Hg or less (other modified qSOFA criteria were Glasgow Coma Scale score <15 and respiratory rate ≥22 breaths per min).[11,12] Participants were categorised by self-reported sex assigned at birth. Participants had to reside within a predefined geographical area to ensure tuberculosis clinic follow-up. We obtained written informed consent from all

participants or surrogates for those without the capacity to provide consent themselves.

Exclusion criteria were known active tuberculosis or receipt of antituberculosis therapy within 6 months of hospitalisation, pregnancy or lactation, allergies to antituberculosis therapy, another investigational drug within the past month, chronic liver disease, heavy alcohol use, positive serum cryptococcal antigen, or clinically significant drug–drug interaction with rifampicin. If, after enrolment, a study participant was found to have baseline grade 4 or 5 renal or hepatic dysfunction, they were excluded for the remainder of the study for safety purposes, but having received at least 1 day of the intervention were included in the intention-to-treat analysis.

The ATLAS trial received approval from the University of Virginia (HSR200253), the Tanzania Medicines and Medical Devices Authority (TMDA-WEB0021/CTR/0008/03) and National Institute for Medical Research (NIMR/HQ/R.8a/Vol. IX/3554), and the Uganda National Council for Science and Technology (HS1272ES). This trial was registered with ClinicalTrials.gov (NCT04618198), and is completed. The protocol is in appendix 1 (pp 34–105).

See Online for appendix 1

### Randomisation and masking

A computer-generated permuted-block algorithm with allocation concealment and random block sizes of four and eight randomly assigned participants (1:1) to receive either immediate or diagnosis-dependent antituberculosis therapy, and (1:1) to receive either high-dose or conventional WHO-recommended weight-based dose antituberculosis therapy. Therefore, the four groups were immediate conventional-dose, immediate high-dose, diagnosis-dependent high-dose, and diagnosis-dependent conventional-dose (standard-of-care) antituberculosis therapy. Allocation was stratified by country and the presence of altered mental status at the time of randomisation. The study statistician generated the randomisation sequence. Participants were screened and enrolled by study nurses, then randomly assigned to trial groups by study doctors. Both nurses and doctors were involved in follow-up study visits.

### Procedures

All participants received 2 g intravenous ceftriaxone daily for 7 days. Participants randomly assigned to conventional WHO-recommended weight-based antituberculosis therapy received fixed-dose combination tablets of rifampicin approximately 10 mg/kg, isoniazid approximately 5 mg/kg, pyrazinamide, and ethambutol, plus pyridoxine 50 mg orally. Participants randomly assigned to receive high-dose antituberculosis therapy received rifampicin approximately 30 mg/kg and isoniazid approximately 7·5 mg/kg as a combination of single formulation tablets and fixed-dose combination tablets that included WHO-recommended weight-based doses of pyrazinamide and ethambutol, plus pyridoxine. Participants continued immediate antituberculosis therapy for 28 days. All medications were administered daily. Participants initiated diagnosis-dependent antituberculosis therapy based on a clinical or microbiological diagnosis of tuberculosis. A clinical diagnosis was defined as no response to ceftriaxone at 3–5 days after randomisation if there was no alternative diagnosis or if showing other features of tuberculosis disease.

Diagnostic testing was done at enrolment. We collected blood and urine for bacterial culture (BACTEC 9050; Becton Dickinson, Franklin Lakes, NJ, USA). To test for tuberculosis, we used Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA, USA) on sputum and urine, Alere Determine LF-LAM (Abbott, Santa Clara, CA, USA) on urine, and mycobacterial culture of sputum (MGIT 960 system; Becton Dickinson, Franklin Lakes, NJ, USA) and blood (BACTEC Myco/F system; Becton Dickinson, Franklin Lakes, NJ, USA). We tested baseline blood samples with a TaqMan Array card (Thermo Fisher, Carlsbad, CA, USA) quantitative PCR assay, which targeted 43 pathogens including *Mycobacterium tuberculosis*, but testing was batched and results were not available to inform clinical decisions.[3]

We monitored participants with clinical assessments daily and laboratory assessments weekly through to day 28. We referred participants who received antituberculosis therapy to a tuberculosis clinic at day 28 where non-study clinicians determined if conventional antituberculosis treatment should continue. An independent data safety monitoring board reviewed interim data at 25%, 50%, and 75% of the target accrual goals. The data safety monitoring board comprised five voting members including the chairperson. Of the voting members, four were clinician-scientists and one was a biostatistician, representing four different institutes in Uganda and Tanzania. An additional non-voting member from the sponsor institute participated in the data safety monitoring board meetings. We based stopping decisions for efficacy on Lan–Demets boundaries.

### Outcomes

The primary efficacy endpoint was mortality at 28 days after randomisation. We defined the survival time for each participant as the time from randomisation until death, discharged (alive) by day 28, or censored (alive) at day 28. The secondary endpoints were time to antituberculosis therapy, defined as the time from randomisation to the first dose of rifampicin; time to temperature normalisation, defined as first measured temperature between 36°C and 38°C; time to ambulation, defined as first report of ambulation; duration of hospitalisation, defined as time from randomisation to discharge; and in-hospital mortality, defined as a participant who died during the hospitalisation of enrolment or was discharged. Other endpoints included adverse drug events during the 28-day study period using the National Institutes of Health Division of AIDS criteria and final sepsis aetiology. The main data for the

prespecified 6-month mortality as defined as time from randomisation to death or alive at 6 months are reported; the detailed data will be reported elsewhere. All outcomes were centrally assessed. Adverse events were systematically assessed at all study timepoints or if the participant had an unplanned presentation to medical care and graded according to recommendations from the National Institutes of Health Division of AIDS.

### Statistical analysis

To calculate the sample size, we assumed that 28-day mortality would be 45% in the diagnosis-dependent conventional-dose group, 32% in the immediate conventional-dose and diagnosis-dependent high-dose groups, and 19% in the immediate high-dose group.[3,5,6,12] A sample size of 437 participants provided 80% power with a two-sided 0·05 significance level to test the effects of time and dose on 28-day mortality, while accounting for 20% loss to follow-up or late exclusions from baseline renal and liver function testing.

The primary analysis was done in the modified intention-to-treat population, including all participants who were randomly assigned and did not meet late exclusion criteria. Subsequent sensitivity analyses were done in the intention-to-treat population, including all randomly assigned participants, with survival time censored at the time of exclusion for those meeting late exclusion criteria. Further sensitivity analyses used inverse probability weighting with several models to predict late exclusion. We did not impute missing data. For the primary outcome, we used Kaplan–Meier curves to estimate survival distribution. We used Cox proportional hazards models on a 28-day timescale to estimate the main effects and interaction of timing and dose, and to compare each group with the standard of care group. In addition to estimating the multiplicative interaction in the Cox models, we also estimated the additive (risk difference) interaction for 28-day mortality risk. We calculated the number needed to treat, with 95% CIs presented as recommended by Altman,[13] as a summary of group differences for the overall study population and in the prespecified subgroup with confirmed tuberculosis. 95% CIs are reported for the number needed to treat where the CIs for the difference in proportions contains zero and the difference between treatments allows for the possibility of either benefit or

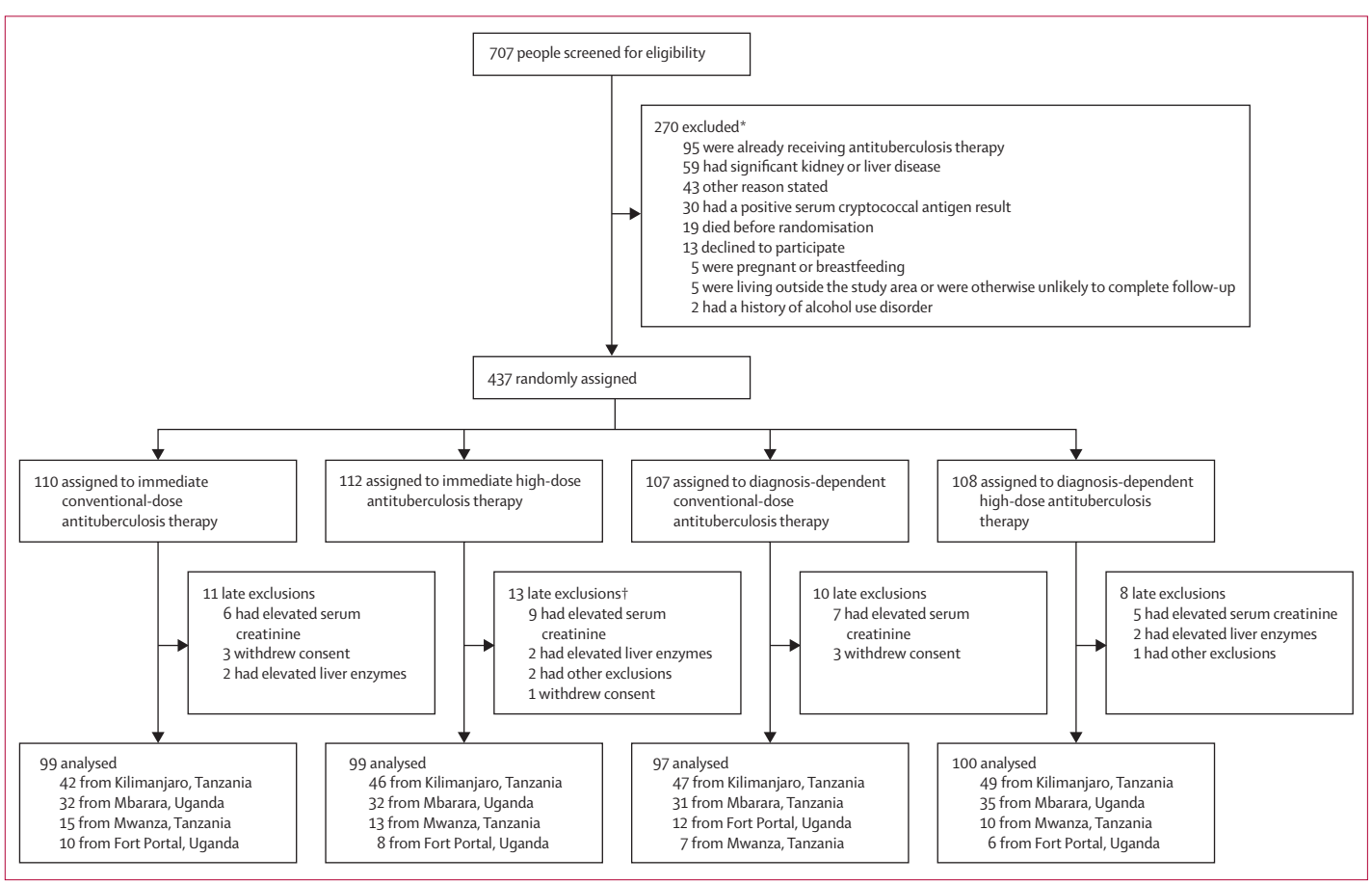



***Figure 1:*** **Trial profile**

*One individual had a positive cryptococcal antigen result and was already receiving antituberculosis therapy. †One participant had both elevated serum creatinine and liver enzymes.

| | Immediate conventional-dose antituberculosis therapy (n=99) | Immediate high-dose antituberculosis therapy (n=99) | Diagnosis-dependent conventional-dose antituberculosis therapy (n=97) | Diagnosis-dependent high-dose antituberculosis therapy (n=100) |
|---|---|---|---|---|
| Age, years | 42 (34–49) | 42 (32–53) | 40 (32–52) | 41 (34–50) |
| Sex | | | | |
| Female | 60 (61%) | 59 (60%) | 52 (54%) | 55 (55%) |
| Male | 39 (39%) | 40 (40%) | 45 (46%) | 45 (45%) |
| Heart rate, beats per min | 115 (97–125) | 121 (103–130) | 120 (101–128) | 121 (109–127) |
| Respiratory rate, breaths per min | 27 (24–30) | 26 (24–30) | 26 (24–30) | 27 (25–32) |
| Systolic blood pressure, mm Hg | 88 (80–90) | 88 (84–90) | 88 (81–90) | 88 (84–90) |
| Diastolic blood pressure, mm Hg | 53 (49–59) | 54 (50–60) | 52 (48–57) | 52 (49–58) |
| Mean arterial blood pressure, mm Hg | 64 (60–69) | 64 (61–70) | 64 (59–67) | 64 (61–69) |
| Oxygen saturation | 96% (92–97) | 95% (90–97) | 96% (92–97) | 95% (92–98) |
| Creatinine, mg/dL | 0·88 (0·67–1·18) | 0·88 (0·64–1·12) | 0·86 (0·62–1·20) | 0·91 (0·64–1·22) |
| Bilirubin total, mg/dL | 0·53 (0·31–0·87) | 0·52 (0·29–0·91) | 0·42 (0·24–1·00) | 0·51 (0·31–0·85) |
| Aspartate aminotransferase, U/L | 45 (27–75) | 42 (28–64) | 51 (27–97) | 37 (25–73) |
| Alanine aminotransferase, U/L | 23 (15–40) | 22 (17–42) | 27 (17–48) | 23 (15–38) |
| BMI, kg/m² | 18·9 (16·7–21·0) | 19·3 (16·8–21·6) | 18·3 (16·2–20·9) | 18·4 (16·8–20·7) |
| Mid-upper arm circumference, cm | 22·0 (20·0–24·0) | 21·9 (20·0–24·9) | 21·6 (19·5–24·0) | 22·4 (20·0–25·0) |
| Glasgow Coma Scale <15 | 30 (30%) | 31 (31%) | 31 (32%) | 31 (31%) |
| qSOFA score | | | | |
| 2 | 86 (87%) | 80 (81%) | 82 (85%) | 83 (83%) |
| 3 | 13 (13%) | 19 (19%) | 15 (15%) | 17 (17%) |
| Universal Vital Assessment score | | | | |
| Median | 5 (4–7) | 5 (4–7) | 5 (4–7) | 5 (4–7) |
| 2–4 | 48 (48%) | 47 (47%) | 51 (53%) | 45 (45%) |
| >4 | 51 (52%) | 52 (53%) | 46 (47%) | 55 (55%) |
| Capillary refill time, s | | | | |
| Median | 3 (1–3) | 3 (1–3) | 3 (1–3) | 3 (2–3) |
| >3 | 6 (6%) | 5 (5%) | 7 (7%) | 7 (7%) |
| Lactate, mmol/L | 2·8 (1·9–4·2) | 2·7 (1·9–3·3) | 2·7 (2·1–3·7) | 2·5 (1·7–3·4) |
| Haemoglobin, g/L | 10·2 (8·6–12·2) | 9·9 (7·9–12·2) | 10·0 (8·1–12·3) | 10·7 (8·4–12·7) |
| CD4⁺ T cells per µL | 92 (21–278) | 138 (43–300) | 147 (43–413) | 132 (31–334) |
| Receiving HIV therapy | 53 (54%) | 39 (39%) | 53 (55%) | 45 (45%) |

Data are median (IQR) or n (%). qSOFA=quick Sequential Organ Failure Assessment.

***Table 1:*** **Baseline characteristics**

harm. For binary outcomes, we used the $\chi^2$ test to compare proportions among the treatment groups. For time-to-event secondary endpoints, we estimated cause-specific hazard ratios (HRs) relative to the standard of care group, treating death as a competing risk. We examined 28-day mortality across predefined subgroups, including microbiologically confirmed tuberculosis diagnosis in the sputum, blood, or urine; categories of immunosuppression (assessed by CD4⁺ T-cell concentration and antiretroviral therapy [ART] at enrolment); disease severity (tissue ischaemia by whole blood lactate concentration and critical illness by Universal Vital Assessment [UVA] mortality risk score[14]); and measures of nutritional status (BMI and mid-upper arm circumference). The $\chi^2$ test was used to compare the proportion of participants in each group with any adverse event, a serious adverse event, or adverse events related to the intervention. Negative binomial regression models were used to compare the number of adverse events per participant among the four groups. We used SAS version 9.4 and GAUSS version 25.0 for analyses.

For more on **GAUSS** see www.aptech.com

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Programme officials and medical monitors from the National Institutes of Health reviewed reports from the data safety monitoring board at predetermined intervals.

## Results

From Jan 5, 2022, to Dec 9, 2024, 707 people were screened for eligibility, 437 of whom were randomly assigned (110 to immediate conventional-dose antituberculosis therapy,

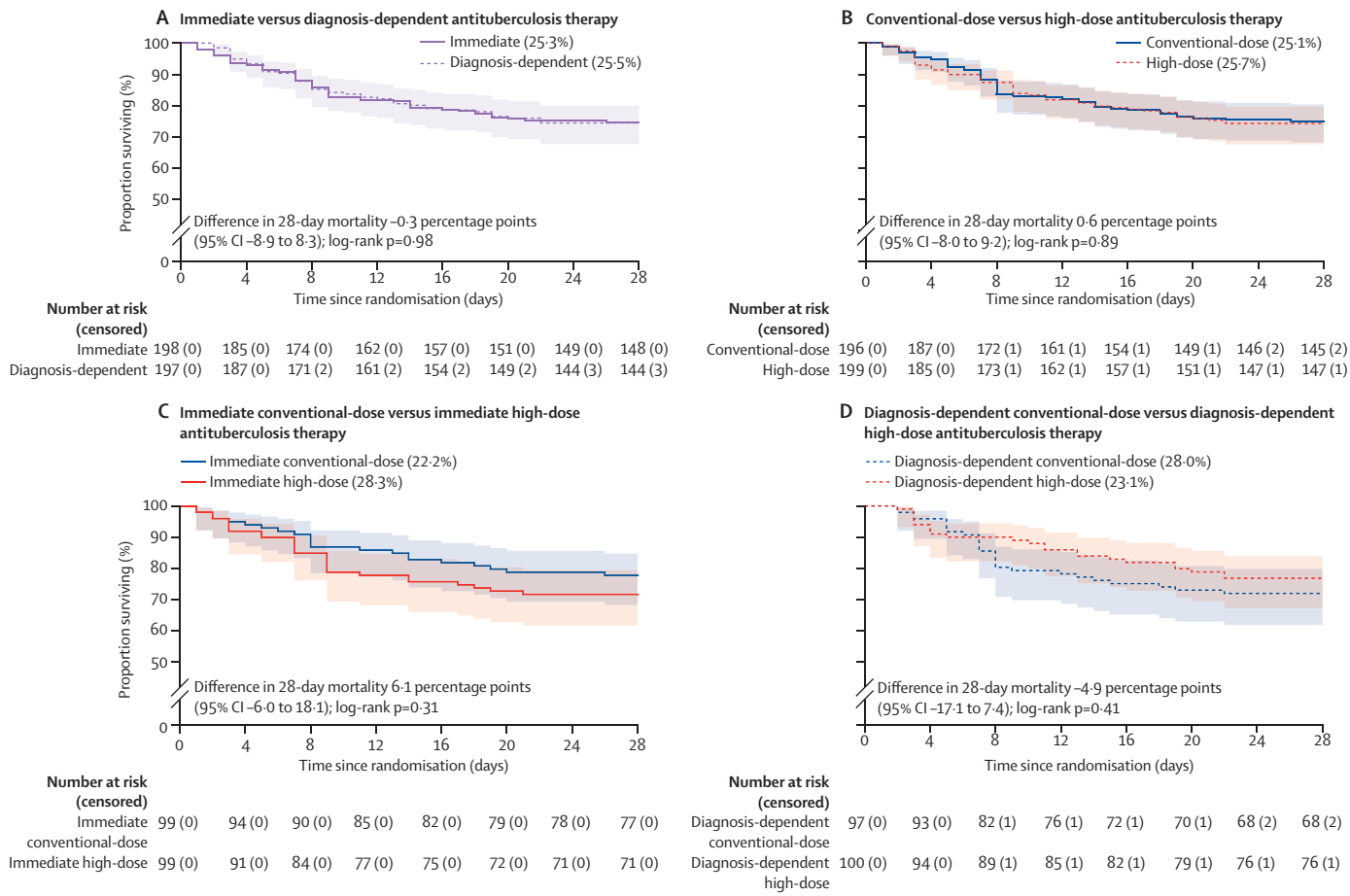



***Figure 2*: 28-day mortality**

(A) 28-day mortality in the immediate versus the diagnosis-dependent antituberculosis therapy groups (both conventional-dose and high-dose). (B) 28–day mortality in the conventional-dose versus high-dose antituberculosis therapy groups (both immediate and dose-dependent). (C) 28-day mortality in the immediate conventional-dose versus the immediate high-dose antituberculosis therapy groups. (D) 28-day mortality in the diagnosis-dependent conventional-dose versus the diagnosis-dependent high-dose antituberculosis therapy groups. Percentages for each group are the day 28 survival proportions, estimated from the Kaplan–Meier curves.

112 to immediate high-dose antituberculosis therapy, 107 to diagnosis-dependent conventional-dose antituberculosis therapy, and 108 to diagnosis-dependent high-dose antituberculosis therapy). There were no major deviations from the protocol. Of the 437 participants, 42 (10%) had late exclusion criteria, leaving 395 who received a study intervention and were analysed for the primary outcome of 28-day mortality (figure 1). Three (1%) participants were lost to follow-up before the day 28 endpoint. Protocol deviations at all four sites were minor and infrequent. The most frequent protocol deviations were reporting of adverse events outside of the specified time window (five [2%] of 268 reports), and study visit procedures deviations, such as not performing chest radiographs or not collecting samples for laboratory testing (21 [1%] of 2506 visits; appendix 1 p 15).

Participant characteristics were similar between the four groups (table 1). Of the 395 participants analysed, 226 (57%) were female, 169 (43%) were male, and the median age was 42 years (IQR 33–51). All participants were categorised as Black race and further tribal or ethnicity information was not collected. 139 (35%) participants had severe undernourishment (BMI ≤16·5 kg/m² or mid-upper arm circumference ≤20·0 cm).

Adjusting for the stratification factors, there was no evidence of differences in 28-day mortality for immediate antituberculosis therapy groups (50 [25%] of 198 patients) compared with diagnosis-dependent groups (50 [25%] of 197 patients; adjusted HR [aHR] 0·99 [95% CI 0·67–1·46]; p=0·95) or for high-dose antituberculosis therapy groups (51 [26%] of 199 patients) compared with conventional-dose groups (49 [25%] of 196 patients; aHR 1·07 [95% CI 0·72–1·59]; p=0·73), with confidence intervals including possibility of benefit or harm (figure 2A, B). The proportional hazards assumption was assessed without significant change in HRs. There was also no evidence of differences in results in the intention-to-treat analyses of all 437 randomly assigned participants (appendix 1

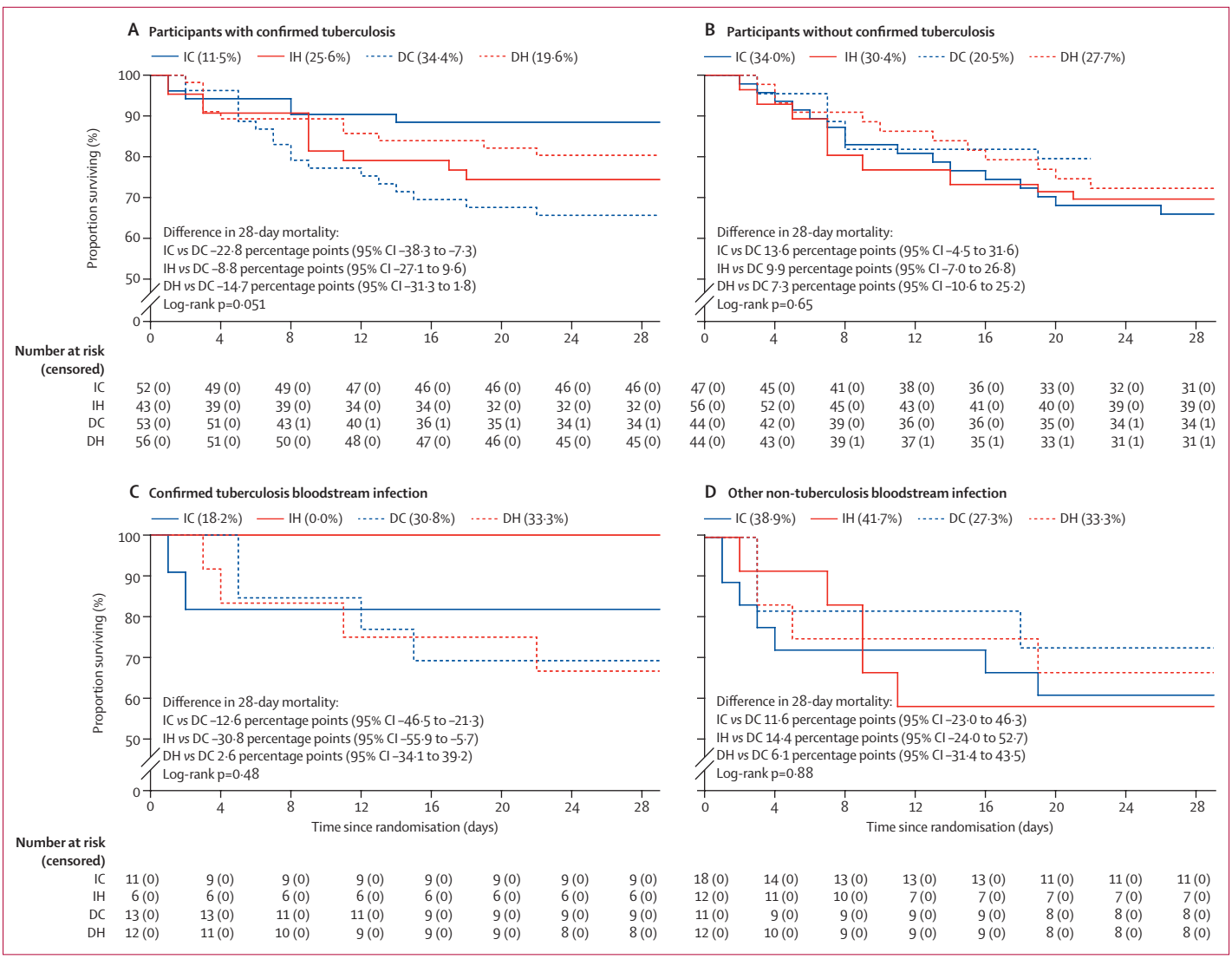



***Figure 3:*** **28-day mortality in participants with and without later confirmed tuberculosis**
(A) 28-day mortality in participants with confirmed tuberculosis. (B) 28-day mortality in participants without confirmed tuberculosis. (C) 28-day mortality in participants with confirmed tuberculosis bloodstream infection. (D) 28-day mortality in participants with other non-tuberculosis bloodstream infection. DC=diagnosis-dependent conventional-dose antituberculosis therapy (standard of care). Percentages for each group are the day 28 mortality proportions, estimated from the Kaplan–Meier curves. DH=diagnosis-dependent high-dose antituberculosis therapy. IC=immediate conventional-dose antituberculosis therapy. IH=immediate high-dose antituberculosis therapy.

pp 16–17). Sensitivity analysis with inverse probability weighting using either stabilised or unstabilised weights, under a number of models for the probability of late exclusions, did not appreciably alter the results (data not shown).

We identified a 10·9 percentage point additive (risk difference) interaction between timing and dosing of antituberculosis therapy such that the lowest 28-day mortality occurred in the immediate conventional-dose and diagnosis-dependent high-dose groups (figure 2, appendix 1 p 18). The 28-day mortality from the censored Kaplan–Meier curve was 22 (22·2% [SE 4·2]) of 99 participants in the immediate conventional-dose group, 23 (23·2% [4·2]) of 100 in the diagnosis-dependent high-dose group, 27 (28·0% [4·6]) of 97 in the diagnosis-dependent conventional-dose (standard of care) group, and 28 (28·3% [4·5]) of 99 in the immediate high-dose group. Compared with the standard of care, the number needed to treat to prevent one death by day 28 was 17·2 (95% CI number needed to harm [NNTH] 15·6 to ∞ to number needed to benefit [NNTB] 5·5) with immediate conventional-dose antituberculosis therapy and 20·8 (95% CI NNTH 13·5 to ∞ to NNTB 5·9) with diagnosis-dependent high-dose antituberculosis therapy (appendix 1 p 19).

We confirmed tuberculosis in 204 (52%) of 395 participants (appendix 1 p 3). Of the 272 (69%) participants with any identified pathogen, 51 (19%) had a

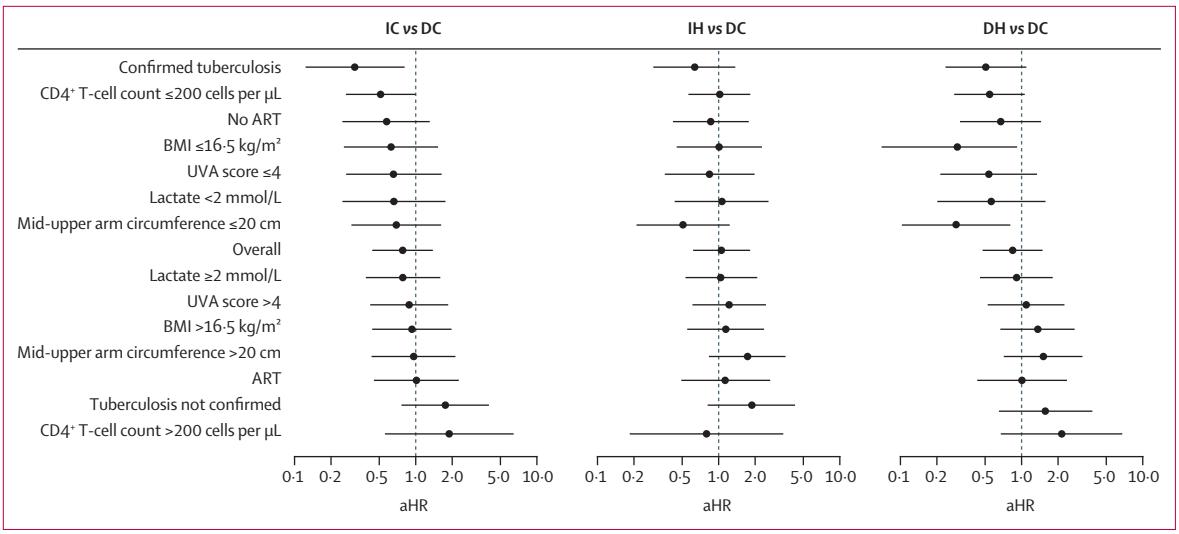



***Figure 4:*** **Forest plots of risk of death at 28 days for prespecified subgroups relative to the standard of care**
aHRs and 95% CI were adjusted for country and altered mental status compared with the standard of care group (DC) to IC, IH, and DH. aHR=adjusted hazard ratio. ART=antiretroviral therapy. DC=diagnosis-dependent conventional-dose antituberculosis therapy (standard of care). DH=diagnosis-dependent high-dose antituberculosis therapy. IC=immediate conventional-dose antituberculosis therapy. IH=immediate high-dose antituberculosis therapy. UVA=Universal Vital Assessment.

| | Immediate conventional-dose antituberculosis therapy (n=99) | Immediate high-dose antituberculosis therapy (n=99) | Diagnosis-dependent conventional-dose antituberculosis therapy (n=97) | Diagnosis-dependent high-dose antituberculosis therapy (n=100) | Total (n=395) | p value |
|---|---|---|---|---|---|---|
| Participants with at least one adverse event | 40 (40%) | 43 (43%) | 39 (40%) | 40 (40%) | 162 (41%) | 0·96 |
| Participants with at least one treatment-related adverse event | 6 (6%) | 13 (13%) | 5 (5%) | 9 (9%) | 33 (8%) | 0·17 |
| Participants with a serious adverse event | 35 (35%) | 37 (37%) | 32 (33%) | 33 (33%) | 137 (35%) | 0·90 |
| Participants with treatment-related and serious adverse events | 4 (4%) | 8 (8%) | 4 (4%) | 6 (6%) | 22 (6%) | 0·37 |

Treatment-related adverse events were classified as possibly, probably, or definitely related to the study intervention. Full details of adverse events are in appendix 1 (pp 10–14).

***Table 2:*** **Adverse events within 28 days of random assignment**

pathogen within the spectrum of activity of ceftriaxone, and 239 (88%) had a pathogen within the spectrum of activity of ceftriaxone or antituberculosis therapy (appendix 1 pp 4–5).[15]

In the subgroup of participants with confirmed tuberculosis, immediate conventional-dose antituberculosis therapy reduced mortality compared with the standard of care, diagnosis-dependent conventional-dose group. The aHR for 28-day mortality relative to the diagnosis-dependent conventional-dose group was 0·32 (95% CI 0·13–0·82; p=0·015) for the immediate conventional-dose group (six [12%] of 51 patients died *vs* 18 [34%] of 53 patients); 0·51 (0·24–1·08; p=0·079) for the diagnosis-dependent high-dose group (11 [20%] of 56 *vs* 18 [34%] 53); and 0·63 (0·29–1·36; p=0·24) for the immediate high-dose group (11 [26%] of 43 *vs* 18 [34%] 53; figure 3A, B, figure 4, appendix 1 pp 6–8, 20–22). The change in risk of death at 28 days with immediate conventional-dose therapy compared with diagnosis-dependent conventional-dose therapy was –23% (95% CI –38 to –7) yielding a number needed to treat to prevent one death of 4·4 (95% CI NNTB 2·6 to 14·3; appendix 1 p 19). The change in risk of death at 28 days with diagnosis-dependent high-dose therapy compared with diagnosis-dependent conventional-dose therapy was –15% (95% CI –31 to 2), yielding a number needed to treat to prevent one death of 6·7 (95% CI NNTH 57·2 to ∞ to NNTB 3·2; appendix 1 p 19).

In further prespecified subgroup analyses of participants who received immediate conventional-dose antituberculosis therapy compared with participants who received diagnosis-dependent conventional-dose antituberculosis therapy, participants with CD4⁺ T-cell concentrations 200 cells per μL or less (16 [24%] of 68 *vs* 22 [37%] of 60 deaths) had an aHR of 0·51 (95% CI 0·27–0·98; p=0·044); those not receiving ART (ten [22%] of 46 *vs* 14 [32%] of 44 deaths) had an aHR of 0·57 (0·25–1·29; p=0·18); those with a BMI of 16·5 kg/m² or less (eight [29%] of 28 *vs* 13 [43%] of 30 deaths) had an aHR of 0·62 (0·26–1·51; p=0·30); those with a UVA score of 4 or less (seven [15%] of 48

*vs* ten [20%] of 51 deaths) had an aHR of 0·66 (0·25–1·74; p=0·40), those with a lactate concentration less than 2 mmol/L (eight [21%] of 39 *vs* 12 [29%] of 41 deaths) had an aHR of 0·66 (0·27–1·62; p=0·36); and those with a mid-upper arm circumference of 20 cm of less (nine [31%] of 29 *vs* 15 [44%] of 34 deaths) had an aHR of 0·69 (0·30–1·60; p=0·39; figure 4; appendix 1 pp 6–8, 23–28).

39 (10%) of 395 patients had tuberculosis bloodstream infection, and 31 (8%) had bloodstream infections from non-tuberculosis pathogens. Among those with tuberculosis bloodstream infection, mortality was lowest in groups receiving immediate antituberculosis therapy, which was not observed among those with non-tuberculosis bloodstream infection (figure 3C, D).

305 (77%) of 395 patients received antituberculosis therapy by day 28. 198 (100%) of 198 patients in the immediate groups received treatment within 24 h of random assignment. By day 28, 107 (54%) of 197 participants in the diagnosis-dependent groups received antituberculosis therapy, of whom 95 (89%) had treatment started within 24 h of random assignment (appendix 1 pp 3, 29). The in-hospital mortality by day 28 was 20 (20%) of 99 patients in the immediate conventional-dose group, 21 (21%) of 100 in the diagnosis-dependent high-dose group, 26 (27%) of 97 in the diagnosis-dependent conventional-dose (standard-of-care) group, and 28 (28%) of 99 in the immediate high-dose group, which did not significantly differ (p=0·44, $\chi^2$ test). Although proportionally more people were discharged by day 28 in the immediate conventional-dose group than in the diagnosis-dependent conventional-dose group, there were no significant differences between any groups in the proportions of participants discharged, ambulating, or with temperature normalisation at 28 days (appendix 1 pp 9, 30–31). At 6 months, mortality rates estimated from censored Kaplan–Meier curves were lowest for those in the immediate conventional-dose (38 [38%] of 99 patients) and diagnosis-dependent high-dose groups (35 [35%] of 100) compared with the standard of care diagnosis-dependent conventional-dose group (40 [41%] of 97) and immediate high-dose group (42 [42%] of 99; appendix 1 pp 32–33). In the subgroup with confirmed tuberculosis, differences in 28-day mortality were sustained at 6 months. Relative to the diagnosis-dependent conventional-dose group (6-month mortality from censored Kaplan–Meier curve of 26 [49%] of 53 patients) the difference in mortality for the immediate conventional-dose group was –22·2% (95% CI –40·6 to –3·8), 6-month mortality from censored Kaplan–Meier curve of 14 (27%) of 52 patients; for the diagnosis-dependent high-dose group the difference was –15·9% (–34·3 to 2·5), 19 (34%) of 56 patients; and for the immediate high-dose group the difference was –6·2% (–28·4 to 15·9), 17 (44%) of 43 patients (appendix 1 pp 32–33). Further analysis of mortality at 6 months will be reported separately.

265 adverse events occurred in the 395 patients within 28 days (table 2; appendix 1 pp 10–13). 162 (41%) patients had at least one adverse event; 137 (35%) had a serious adverse event. There was no significant difference among the four intervention groups regarding the number of adverse events, the number of serious adverse events, or the number of treatment-related adverse events. However, there were numerically more adverse events of drug-induced liver injury (appendix 1 pp 10, 13), and a greater number of participants with at least one episode of increased alanine aminotransferase and aspartate aminotransferase levels in the immediate high-dose group than in any other group, and increased total bilirubin in both high-dose groups compared with both conventional-dose groups (appendix 1 pp 11–12).

## Discussion

Unlike trials of sepsis outside of Africa where a pathogen is identified in the minority, the ATLAS trial in adults with HIV-related sepsis in east Africa found a plausible pathogen in nearly 70% of patients. Tuberculosis was found in more than half of the population and was the most common pathogen.[15] Yet, when analysed as the main effects, antituberculosis treatment delivered immediately or at high dose did not significantly reduce 28-day mortality among all participants. When examined by randomisation group, the absence of difference between those receiving immediate versus diagnosis-dependent antituberculosis therapy, and the absence of difference between those receiving conventional-dose versus high-dose antituberculosis therapy appeared to be driven by an interaction between immediate timing and higher dose. Accordingly, the lowest overall mortality was observed in the immediate conventional-dose and diagnosis-dependent high-dose groups. Despite clinically significant immunocompromise and critical illness, overall 28-day mortality was lower than expected, and might reflect the high proportion of participants ultimately treated for tuberculosis in all groups.[4,6]

In the prespecified subgroup with confirmed tuberculosis, immediate conventional-dose antituberculosis therapy improved 28-day mortality compared with standard of care, with a number needed to treat to prevent one death of 4·4 people. The lower 28-day mortality in the immediate conventional-dose group was likely a result of immediately treating difficult-to-diagnose tuberculosis, including bloodstream infection, that was frequently missed with rapid diagnostic tests.[16] This was further supported by lower 28-day mortality in participants with more severe immunocompromise in whom underlying tuberculosis was more likely, including those with a $CD4^+$ T-cell concentration of 200 cells per µL or less, or those who were not on ART at presentation.[16,17] These findings align with other retrospective studies of patients with tuberculosis sepsis in which negative treatment outcomes were observed from delays measured in hours in initiating antituberculosis therapy,[12,18] but are unlike previous trials of ambulatory people living with HIV with

suspected tuberculosis, which did not show a benefit in empiric tuberculosis treatment.[19–21] This suggests that even hours to pathogen-targeted therapy might matter for those with tuberculosis sepsis.[18]

Lower mortality with immediate conventional-dose tuberculosis treatment in those with later diagnosed tuberculosis carries several important implications: *M tuberculosis* is a likely causative pathogen of sepsis, frequently associated with bloodstream infection in people living with HIV, and not only a chronic disease; and current diagnostic tests appear inadequate to guide a rapid enough start of targeted treatment for the full spectrum of tuberculosis infection. Novel diagnostics for tuberculosis are in various stages of development, but these have prioritised ambulatory patients. Currently approved rapid diagnostics are often unavailable in hospital settings where people living with HIV present for critical care and are anticipated to be less accessible with the recent loss of global funding.[8] A strategy of immediate empirical antituberculosis therapy in this patient population could potentially contribute to antimicrobial resistance; however, rifampicin is the only first-line antituberculosis drug that might also be used to treat non-mycobacterial disease. Typically, rifampicin is given as adjunct therapy in these situations, so the overall impact on resistance development and the treatment of clinical infection would likely be minimal.

To our knowledge, the ATLAS trial is the first to use 30 mg/kg of rifampicin and 7·5 mg/kg of isoniazid in people living with HIV with available oral formulations among a critically ill population. However, immediate high-dose antituberculosis therapy did not appear to benefit all patients with confirmed tuberculosis in contradistinction to our understanding that higher serum exposures of bactericidal antituberculosis drugs can hasten *M tuberculosis* killing in people with pulmonary disease. Importantly, these findings reflect similar results of two related trials in people with disseminated tuberculosis and tuberculous meningitis. In the NewStrat-TB trial,[22] which evaluated 35 mg/kg of oral rifampicin doses combined with levofloxacin and corticosteroids to intensify treatment in inpatients with disseminated tuberculosis in South Africa, an early conference report suggested that the intensified regimen was associated with a higher 2-week mortality.[23] In the HARVEST trial,[24] participants were randomly assigned to 35 mg/kg of oral rifampicin for tuberculosis meningitis in addition to standard of care combination antituberculosis therapy and corticosteroids. The HARVEST trial found no benefit from higher dose rifampicin for the primary outcome of 6-month mortality, and, in the subgroup with HIV on ART, a higher mortality occurred in those receiving high-dose compared with conventional-dose rifampicin.[24]

We hypothesise that rapid killing of *M tuberculosis* by immediate high-dose antituberculosis therapy might have provoked a deleterious hyperinflammatory immune response in participants with confirmed tuberculosis in the ATLAS participants.[25] It is also possible that immediate high-dose rifampicin contributed to adrenal crises in participants with critical illness-related corticosteroid insufficiency through increased metabolism of endogenous corticosteroids,[26] an interaction that might also explain findings in the NewStrat-TB[22,23] and HARVEST[24] trials in those groups receiving exogenous corticosteroids. Additional pharmacokinetic and immunological studies from ATLAS are planned.

Although there were no safety concerns in the conventional-dose groups of ATLAS, a numerically higher number of adverse events of drug-induced liver injury occurred in the group receiving immediate high-dose antituberculosis treatment. In trials of adults with pulmonary tuberculosis, rifampicin oral doses of up to 35 mg/kg did not lead to severe hepatotoxicity;[27,28] however, mild gastrointestinal symptoms and hyperbilirubinaemia have been observed in a dose-dependent manner. The HARVEST trial[24] also reported that hyperbilirubinaemia occurred significantly more frequently in the high-dose rifampicin group and the number of drug-induced liver injuries were also numerically more frequent compared with the conventional-dose group, suggesting, along with ATLAS findings, that higher dose rifampicin might be harmful in critically ill populations.

Although the ATLAS trial examined two pharmacological interventions, antituberculosis timing and dose, in a representative population from diverse regions within two east African countries, and obtained nearly complete retention of participants, adherence to trial interventions, and ascertainment of all trial endpoints, there were several limitations. Scoring systems for sepsis have shown variable capacity for predicting disease severity and mortality.[29] The UVA score has been shown to provide additional predictive value for mortality compared with qSOFA for patients in Africa,[14,30] thus we used the UVA score to further stratify severity of illness and risk of death among participants who met modified qSOFA criteria, rather than using the UVA score as an inclusion criterion. Nevertheless, the observed mortality estimates for the standard of care group were lower than estimated in the trial design, suggesting a loss of power for determining differences in the main effects. In a previous study of sepsis from Uganda, the 26% mortality for non-tuberculosis pathogens was similar to that of all ATLAS groups without confirmed tuberculosis.[3] Although biologically plausible and suggestive that the improvement in mortality within the subgroup with later confirmed tuberculosis was related to the intervention and not overall standard of care in a trial setting,[17] the persistently unchanged mortality in those without tuberculosis might be attributed to other ceftriaxone-resistant pathogens, such as those found in 25% of ATLAS participants with any identified

non-tuberculosis pathogen. This observation suggests the need to carefully re-examine the role of empirical ceftriaxone in this patient population. Given that there were no anticipated sex-based differences in 28-day mortality, this was not a prespecified subgroup analysis, and although all participants were of the same racial categorisation, no further tribal or ethnicity affiliation was collected. The secondary outcome of mortality at 6 months showed similar trends among treatment groups to the primary outcome at 28 days as well as in the subgroup with later confirmed tuberculosis, but, given important differences in non-study clinicians' decisions to continue tuberculosis treatment in those without confirmed diagnoses after 28 days, those data will be more fully reported separately. Last, despite balance across baseline characteristics, there was a lower number of participants with confirmed tuberculosis in the immediate high-dose group, which might have contributed to the discrepant finding of trends of improved mortality for those with *M tuberculosis* bloodstream infection but lack of benefit across all participants in the group.

Of the 30 WHO-designated high co-burden tuberculosis–HIV countries in 2025, 22 are in Africa. In ATLAS participants, tuberculosis was the most common aetiology of sepsis and diagnosed in the majority, including those with bloodstream infection that would have otherwise been missed with rapid diagnostics. Although there was no overall benefit in immediate or high-dose antituberculosis therapy, in prespecified subgroup analysis, immediate conventional-dose antituberculosis therapy led to a significant reduction in 28-day mortality among those with later confirmed tuberculosis, whereas immediate high-dose therapy did not, in alignment with emerging evidence in other populations with advanced HIV and extra-pulmonary tuberculosis.

#### Contributors

Conceptualisation and study design: SKH, SGM, CM, and CCM. Data collection: EN, BS, MN, RA, RM, PB, AMN, DM, GG, SJ, AG, AGR, DO, JK, OA, DKM, LA, BM, and MS. Investigation: PB, AMN, DM, GG, SJ, AG, AGR, JK, OA, DO, DKM, and FCM. Data analysis: SKH, SGM, CM, CCM, EN, BS, MC, MN, TAT, EO, LA, BM, PR, AL, JL, and LE. Data interpretation: SKH, SGM, CM, CCM, EN, BS, MC, MN, TAT, and DRB. Validation: SKH, MC, and MN. Writing: SKH, SGM, EN, BS, TAT, DRB, CM, and CCM. Project administration: MN, EN, BS, PR, AL, and BM. Supervision: FCM. Funding acquisition: SKH, TAT, and CCM. SKH, SGM, MC, MN, CM, and CCM accessed and verified all the data. SKH, SGM, CM, and CCM were responsible for the decision to submit the manuscript. All authors reviewed and approved this manuscript before submission, had access to the data, and have final responsibility for the decision to submit for publication.

#### Equitable partnership declaration

The authors of this paper have submitted an Equitable Partnership Declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of The Lancet Group's broader goal to decolonise global health.

See Online for appendix 2

#### Declaration of interests

SKH, TAT, and CCM report grants paid to their institution to support the work reported in this manuscript (U01 AI150508, D43 TW012247, R21 AI172637, and K24 AI187675). All other authors declare no competing interests.

#### Data sharing

Individual participant data from the ATLAS trial will be made available to researchers on request to the study principal investigators (SKH [skh8r@uvahealth.org] and CCM [ccm5u@uvahealth.org]). Data will be shared within 1 year of study conclusion, and requests should include a plan for use. Supporting materials, including the full study protocol, will be provided to facilitate appropriate secondary analyses.

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#### References

1 Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; **315:** 801–10.
2 Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; **395:** 200–11.
3 Moore CC, Jacob ST, Banura P, et al. Etiology of sepsis in Uganda using a quantitative polymerase chain reaction-based TaqMan array card. *Clin Infect Dis* 2019; **68:** 266–72.
4 Lewis JM, Feasey NA, Rylance J. Aetiology and outcomes of sepsis in adults in sub-Saharan Africa: a systematic review and meta-analysis. *Crit Care* 2019; **23:** 212.
5 Andrews B, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, Bernard GR. Simplified severe sepsis protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia. *Crit Care Med* 2014; **42:** 2315–24.
6 Andrews B, Semler MW, Muchemwa L, et al. Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension: a randomized clinical trial. *JAMA* 2017; **318:** 1233–40.
7 WHO Knowledge Action Portal on NCDs. Operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities, third edition. https://knowledge-action-portal.com/en/content/operational-handbook-tuberculosis-module-6-tuberculosis-and-comorbidities-third-edition (accessed Sept 29, 2025).
8 Aguiar Soares K, Ehrlich J, Camará M, et al. Implementation of WHO guidelines on urine lateral flow LAM testing in high TB/HIV burden African countries. *Eur Respir J* 2023; **62:** 2300556.
9 Rao PS, Moore CC, Mbonde AA, et al. Population pharmacokinetics and significant under-dosing of anti-tuberculosis medications in people with HIV and critical illness. *Antibiotics (Basel)* 2021; **10:** 739.
10 Said B, Nuwagira E, Liyoyo A, et al. Early empiric anti-*Mycobacterium tuberculosis* therapy for sepsis in sub-Saharan Africa: a protocol of a randomised clinical trial. *BMJ Open* 2022; **12:** e061953.
11 Rudd KE, Seymour CW, Aluisio AR, et al. Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score with excess hospital mortality in adults with suspected infection in low- and middle-income countries. *JAMA* 2018; **319:** 2202–11.
12 Hazard RH, Kagina P, Kitayimbwa R, et al. Effect of empiric anti-*Mycobacterium tuberculosis* therapy on survival among human immunodeficiency virus-infected adults admitted with sepsis to a regional referral hospital in Uganda. *Open Forum Infect Dis* 2019; **6:** ofz140.
13 Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998; **317:** 1309–12.
14 Moore CC, Hazard R, Saulters KJ, et al. Derivation and validation of a universal vital assessment (UVA) score: a tool for predicting mortality in adult hospitalised patients in sub-Saharan Africa. *BMJ Glob Health* 2017; **2:** e000344.
15 Otoupalova E, Ampaire L, Null M, et al. Aetiology of sepsis in adults living with HIV in East Africa: a secondary analysis of an open-label, multicentre, randomised, controlled, phase 3 trial. *eClinicalMedicine* 2026; published online Jan 28. https://doi.org/10.1016/j.eclinm.2025.103719.
16 Sindato EM, Mlwati A, Swai SS, Kajogoo VD. Postmortem for intensified missed tuberculosis case finding in high human immunodeficiency virus and tuberculosis-burdened settings in sub-Saharan Africa among adults' population: systematic review and meta-analysis. *Int J Mycobacteriol* 2024; **13:** 126–32.

17 Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010; **340:** c117.

18 Kethireddy S, Light RB, Mirzanejad Y, et al. *Mycobacterium tuberculosis* septic shock. *Chest* 2013; **144:** 474–82.

19 Hosseinipour MC, Bisson GP, Miyahara S, et al. Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial. *Lancet* 2016; **387:** 1198–209.

20 Blanc F-X, Badje AD, Bonnet M, et al. Systematic or test-guided treatment for tuberculosis in HIV-infected adults. *N Engl J Med* 2020; **382:** 2397–410.

21 Manabe YC, Worodria W, van Leth F, et al. Prevention of early mortality by presumptive tuberculosis therapy study: an open label, randomized controlled trial. *Am J Trop Med Hyg* 2016; **95:** 1265–71.

22 Namale PE, Boloko L, Vermeulen M, et al. Testing novel strategies for patients hospitalised with HIV-associated disseminated tuberculosis (NewStrat-TB): protocol for a randomised controlled trial. *Trials* 2024; **25:** 311.

23 Meintjes G, Namale P, Barr D, et al. Supplemental high-dose rifampicin and levofloxacin for inpatients with disseminated HIV-TB. Conference on Retroviruses and Opportunistic Infections; March 9–12, 2025 (abstr 114).

24 Meya DB, Cresswell FV, Dai B, et al. Trial of high-dose oral rifampin in adults with tuberculosis meningitis. *N Engl J Med* 2025; **393:** 2434–46.

25 Tiwari D, Martineau AR. Inflammation-mediated tissue damage in pulmonary tuberculosis and host-directed therapeutic strategies. *Semin Immunol* 2023; **65:** 101672.

26 Keven K, Uysal AR, Erdogan G. Adrenal function during tuberculous infection and effects of antituberculosis treatment on endogenous and exogenous steroids. *Int J Tuberc Lung Dis* 1998; **2:** 419–24.

27 Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis* 2017; **17:** 39–49.

28 Svensson EM, Dian S, Te Brake L, et al. Model-based meta-analysis of rifampicin exposure and mortality in Indonesian tuberculous meningitis trials. *Clin Infect Dis* 2020; **71:** 1817–23.

29 Adegbite BR, Edoa JR, Ndzebe Ndoumba WF, et al. A comparison of different scores for diagnosis and mortality prediction of adults with sepsis in low-and-middle-income countries: a systematic review and meta-analysis. *EClinicalMedicine* 2021; **42:** 101184.

30 Lal S, Luangraj M, Keddie SH, et al. Predicting mortality in febrile adults: comparative performance of the MEWS, qSOFA, and UVA scores using prospectively collected data among patients in four health-care sites in sub-Saharan Africa and south-eastern Asia. *EClinicalMedicine* 2024; **77:** 102856.