

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract Our study design is indicated in the title and abstract (prospective cohort study) (b) Provide in the abstract an informative and balanced summary of what was done and what was found We provide details of what was done and our findings in the abstract: Methods and Findings
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported We provide background and rationale for the investigation: Section: Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses We state the objectives and hypothesis in the Introduction section, last paragraph
Methods		
Study design	4	Present key elements of study design early in the paper We present the study design in the first paragraph of the Methods section: Study design and Setting.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection We present the setting, location, recruitment dates, follow-up time, methods of follow-up and data collection in the Methods section: Study design and setting, Participants, Data collection and definitions.
Participants	6	(a) <i>Cohort study</i>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up We provide these details in Methods section: Participants. <i>Case-control study</i>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i>—For matched studies, give matching criteria and number of exposed and unexposed Not applicable <i>Case-control study</i>—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable We provide these details in the Methods section: Data collection and definitions.
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group

We provide these details in the Methods section: Data collection and definitions and Laboratory assays.		
Bias	9	Describe any efforts to address potential sources of bias We used a random selection method if there were more potentially eligible patients than we had capacity to enrol (Methods section: Participants). We randomly selected samples to test immunological markers (Methods section: Laboratory Assays).
Study size	10	Explain how the study size was arrived at The sample size calculations were performed for major experiments in the original protocol. We include this in the Methods section: Statistical analysis, first paragraph
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why We describe this in the Methods section: Statistical analysis.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding We describe this in the Methods section: Statistical analysis.
		(b) Describe any methods used to examine subgroups and interactions We describe this in the Methods: Statistical analysis section
		(c) Explain how missing data were addressed We describe this in the Methods section: Laboratory assays and Statistical analysis. Details about missing data is included in the footnotes of tables where relevant.
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed We describe this in the Methods section: Statistical analysis, first paragraph <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy
		(e) Describe any sensitivity analyses We describe this in the Methods section: Statistical analysis (second last paragraph) and Results section: Variance of host soluble inflammatory mediators.

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed We report this in the Results section: Participant characteristics and mortality and Figure 1. (b) Give reasons for non-participation at each stage We report this in Figure 1. (c) Consider use of a flow diagram See Figure 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders We provide this in the Results section: Participant characteristics and mortality, and Table 2 (b) Indicate number of participants with missing data for each variable of interest We provide this in Results section: Participant characteristics and mortality and Table 2. (c) <i>Cohort study</i>—Summarise follow-up time (eg, average and total amount) All patients were followed up for 12 weeks. 12-week outcome was ascertained, and we provide this data in the Methods section: Participants (last paragraph) and Data collection and definitions (first paragraph).
Outcome data	15*	<i>Cohort study</i>—Report numbers of outcome events or summary measures over time We provide this in the Results section: Participant characteristics and mortality and Table 2. <i>Case-control study</i>—Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i>—Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included We report raw and adjusted p-values and 95% confidence intervals where appropriate throughout the Results section and in the legends of relevant figures. (b) Report category boundaries when continuous variables were categorized We report the category boundaries in the Cox proportional hazards models where we categorized age and HIV viral load: Results section: Variance of host soluble inflammatory mediators and Figure 5. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not applicable.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses We describe all analyses in detail in the Methods section: Statistical analysis and in the figure legends. We also describe a sensitivity analysis performed on request of a reviewer in the Methods section: Statistical analyses (second last paragraph) and Results: Variance of host soluble inflammatory mediators.
Discussion		
Key results	18	Summarise key results with reference to study objectives We summarised our findings in the first paragraph of the Discussion section.

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias We discuss the limitations of the study in the Discussion section, paragraph 11.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence We compare our finding with other studies in the field and give cautious interpretation of findings throughout the Discussion section.
Generalisability	21	Discuss the generalisability (external validity) of the study results We discuss generalizability of these results in the Discussion section under strengths, paragraph 12.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based We provide details of funding and the role of the funders separately as requested by this journal. We also include the original study protocol. This paper constitutes the main study results.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

S1 Table: Criteria used to classify participants with probable tuberculosis

Probable tuberculosis	Number
Tuberculosis not microbiologically confirmed and urine LAM positive	18
Tuberculosis not microbiologically confirmed; urine LAM negative; pleural effusion which was treated for tuberculosis or exudative pleural effusion with adenosine deaminase >30g/dL and no alternative diagnosis made	21
Tuberculosis not microbiologically confirmed; urine LAM negative; pericardial effusion treated for tuberculosis and no alternative diagnosis made	3
Tuberculosis not microbiologically confirmed; urine LAM negative; miliary tuberculosis on chest X-ray treated for tuberculosis and no alternative diagnosis made	6
Tuberculosis not microbiologically confirmed; urine LAM negative; features of tuberculosis on abdominal ultrasound (multiregion nodes ≥ 1 cm diameter or splenic microabscesses) treated for tuberculosis and no alternative diagnosis made	3
Tuberculosis not microbiologically confirmed; urine LAM negative; cerebrospinal fluid (CSF) picture compatible with probable tuberculous meningitis (TBM) with CSF score ≥ 2 out of 4 [1]), treated for TBM and no alternative diagnosis made.	9
Tuberculosis not microbiologically confirmed; urine LAM negative; computed tomography (CT) scan features of central nervous system tuberculosis, treated for tuberculosis with no alternative diagnosis made	1
Tuberculosis not microbiologically confirmed; urine LAM negative; compatible chest X-ray, treated for tuberculosis and remained on treatment	28
Total	89

S1 Table: Patients who did not have microbiologically confirmed tuberculosis were assessed for features compatible with tuberculosis and classified as probable tuberculosis, possible tuberculosis or no tuberculosis (see also Supplementary Table 2). Participants with probable tuberculosis were included in the analysis along with participants with microbiologically confirmed tuberculosis.

1. Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect Dis* **2010**; 10(11): 803-12.

S2 Table: Exclusions: Details of participants with no tuberculosis and possible tuberculosis:

No tuberculosis	Number
Tuberculosis not microbiologically confirmed; urine LAM negative and disseminated <i>cryptococcosis</i>	6
Tuberculosis not microbiologically confirmed; urine LAM negative and culture proven bacterial bloodstream infection	9
Tuberculosis not microbiologically confirmed; urine LAM negative and clinical diagnosis of community acquired pneumonia with no criteria for clinical tuberculosis and improved without antituberculosis treatment	33
Tuberculosis not microbiologically confirmed; urine LAM negative and treated for <i>Pneumocystis jiroveci</i> pneumonia, not treated for tuberculosis and improved or <i>P. jiroveci</i> diagnosed on post mortem	6
Tuberculosis not microbiologically confirmed; urine LAM negative and no criteria for clinical tuberculosis with alternative diagnosis confirmed (examples, malignancy or venous thromboembolism)	15
Possible tuberculosis	
Tuberculosis not microbiologically confirmed; urine LAM negative and clinical suspicion of tuberculosis together with or indistinguishable from a second infection; neither infection proven; treated for both.	14

S2 Table: Patients without microbiologically confirmed tuberculosis were assessed for features compatible with tuberculosis and classified as probable tuberculosis, possible tuberculosis or no tuberculosis (see also S1 Table). Participants with possible and no tuberculosis were excluded from analysis.

S3 Table: Cox proportional hazards analysis evaluating association of cytomegalovirus viraemia with mortality:

Variable	Hazard Ratio (95% CI)	p	Adjusted Hazard Ratio (95% CI)	p
CMV viral load detectable	1.50 (0.95-2.30)	0.081	1.37 (0.87-2.17)	0.171
Age (per 5-year increase)	1.30 (1.10-1.40)	<0.001	1.30 (1.17-1.44)	<0.001
Male sex	1.00 (0.65-1.60)	0.980	0.94 (0.60-1.48)	0.790
HIV Viral Load (per 1000 copies/ml increase)	1.00 (1.00-1.00)	0.370	1.00 (1.00-1.00)	0.310
CD4 count (per 10 cells increase)	0.96 (0.93-0.99)	0.014	0.96 (0.93-0.99)	0.014

S3 Table: The relationship between cytomegalovirus infection and outcome may be confounded by HIV related factors and immunosuppression. A Cox proportional hazards analysis was performed and each variable was evaluated individually (unadjusted) and then in a multivariate model including for age, sex, HIV viral load and CD4 count to adjust for patient specific variance and HIV-related factors. The model was censored at 28 days to meet the proportional hazards assumption and the global proportional hazards test for the multivariable model result was p=0.75.

S4 Table: Host soluble mediators of inflammation values in hospitalized HIV-TB co-infected participants: Comparison between early deaths (within 7 days after enrolment) and survivors

	Early Deaths n=46	Survivors n=391	p	Holms-Bonferroni p
Higher in participants who died early				
IL-8	428.5 [195.5, 1197.8]	110.0 [78.5, 165.5]	<0.001	<0.001
IL-1Ra	1417.0 [449.8, 3866.0]	169.5 [93.0, 397.5]	<0.001	<0.001
MIP-1 β /CCL4	1809.0 [917.0, 4051.3]	624.5 [397.5, 1087.5]	<0.001	<0.001
IP-10/CXCL10	16911.0 [8412.5, 22836.3]	6495.0 [3301.5, 11846.3]	<0.001	<0.001
IL-6	590.0 [244.0, 1092.3]	208.0 [119.3, 359.8]	<0.001	<0.001
RANTES/CCL5	10728.5 [4928.8, 13834.0]	15369.5 [12732.5, 16552.3]	<0.001	<0.001
MIP-1 α /CCL3	248.0 [92.3, 462.0]	93.0 [65.8, 156.3]	<0.001	<0.001
MCP-1/CCL2	153.0 [87.0, 453.0]	95.5 [75.0, 138.0]	<0.001	0.012
IL-9	189.0 [146.0, 435.5]	153.0 [121.0, 205.0]	0.001	0.029
Lower in participants who died early				
IL-13	24.0 [17.5, 32.5]	39.0 [29.0, 59.5]	<0.001	<0.001
PDGF	72.0 [55.5, 133.3]	201.0 [84.0, 418.5]	<0.001	<0.001
IL-5	18.0 [13.5, 25.0]	31.0 [22.0, 43.5]	<0.001	<0.001
IL-7	26.0 [22.0, 31.8]	35.0 [28.0, 45.3]	<0.001	0.004
IL-12p70	43.5 [34.5, 56.8]	56.0 [42.0, 76.8]	0.001	0.037
No difference between early deaths and survivors				
FGF	44.0 [38.0, 57.0]	54.0 [43.8, 69.0]	0.004	0.118
G-CSF/CSF3	91.0 [51.5, 218.3]	67.0 [54.0, 90.5]	0.015	0.407
*TGF- β 1	18.1 [14.2, 32.4]	26.4 [15.7, 53.9]	0.020	0.571
IL-4	41.0 [28.5, 57.8]	48.0 [36.8, 63.3]	0.059	1.000
IL-15	104.0 [75.0, 133.5]	89.5 [74.0, 114.3]	0.078	1.000

IL-1 β	69.5 [57.3, 122.0]	64.0 [50.0, 84.5]	0.104	1.000
IL-17	56.0 [42.5, 85.8]	64.5 [48.8, 90.3]	0.181	1.000
IL-10	80.5 [53.5, 115.5]	69.0 [55.0, 85.0]	0.201	1.000
VEGF	114.5 [64.5, 150.5]	107.0 [78.8, 158.8]	0.446	1.000
Eotaxin	69.5 [45.0, 136.3]	66.0 [53.0, 88.3]	0.592	1.000
IFN γ	52.0 [33.5, 79.5]	54.0 [39.0, 74.5]	0.663	1.000
GM-CSF/CSF2	88.0 [68.3, 116.3]	89.5 [72.0, 113.0]	0.895	1.000
TNF α	43.0 [31.5, 60.0]	43.5 [36.0, 54.3]	0.914	1.000
IL-2	66.0 [50.8, 87.0]	68.0 [55.3, 81.0]	0.988	1.000

S4 Table: Host soluble inflammatory mediators were measured in a random selection of participants with HIV-associated tuberculosis (n= 46 early deaths and n=391 survivors) using the Biorad Bioplex 200 Luminex platform, except for transforming growth factor beta 1 (TGF- β 1) concentrations which were measured with enzyme-linked immunosorbent assay (ELISA). This table shows differences between early deaths and survivors. Inflammatory mediators are arranged into three groups: Mediators which were higher in early deaths, mediators which were lower in early deaths and mediators which showed no difference between survival groups. Each group is ranked from lowest to highest p-values. Fluorescence index values are presented for all mediators except *TGF- β 1 which is presented in picogram per millilitre. Comparisons between early deaths and survivors were made using the Wilcoxon rank sum test. P-values were corrected for multiple comparisons with Holms-Bonferroni correction. Bold p-values indicate mediators which remained significantly different after correction for multiple comparisons.

IL: interleukin, MIP: monocyte inflammatory protein, CCL: chemokine (C-C motif) ligand, Ra: receptor antagonist, IP-10: interferon gamma induced protein, CXCL: C-X-C motif chemokine, MIP: macrophage inflammatory protein, MCP: monocyte chemoattractant protein, RANTES: regulated on activation, normal T cell expressed and secreted, PDGF: platelet-derived growth factor, FGF: *fibroblast growth factor*, IFN γ : interferon gamma, TNF α : tumour necrosis factor alpha, GM-CSF: granulocyte-macrophage colony-stimulating factor, CSF2: colony stimulating factor 2, VEGF: vascular endothelial growth factor, G-CSF: granulocyte-colony stimulating factor, CSF3: colony stimulating factor 3

S5 Table: Hospitalized patients with HIV-associated tuberculosis: Bacterial culture results from urine, sputum, stool and other anatomical sites

		Died n=124	Survived n=443	p
Urine bacterial culture	<i>Enterococcus</i> species	2 (1.6)	3 (0.7)	0.924
	Gram negative organism	2 (1.6)	2 (0.5)	
	Yeast	5 (4)	9 (2)	
Sputum bacterial culture	<i>Candida albicans</i>	2 (1.6)	6 (1.4)	0.202
	Gram negative organism	3 (2.4)	3 (0.7)	
	<i>Moraxella catarrhalis</i>	0	1 (0.2)	
	<i>Rhizopus</i> species	0	1 (0.2)	
	<i>Staphylococcus aureus</i>	0	9 (2.0)	
	Mixed oral flora	7 (5.6)	38 (8.6)	
<i>Clostridium difficile</i> test in stool	Positive	2 (1.6)	6 (1.4)	1.000

S5 Table: Results for all bacterial cultures which were performed in hospital were captured. The study team performed sputum bacterial cultures on patients when sufficient sputum was obtained to perform tuberculosis tests and bacterial culture. All other tests were performed in routine service by the medical teams as clinically indicated.

Results presented as n (%).

Fisher's exact test used to compare proportions.

n= 105 patients had urine bacterial culture performed

n= 312 patients had sputum bacterial culture performed

n= 27 patients had pleural fluid bacterial culture performed: no sample had a positive bacterial culture

n= 154 patients had cerebrospinal fluid (CSF) bacterial culture performed: 3 patients had a positive culture:

One patient with clinical tuberculosis cultured *Neisseria meningitidis* in CSF and survived.

One patient with microbiologically proven TB cultured *Bacillus* species in CSF and survived.

One patient with microbiologically proven TB cultured *Pseudomonas putida* in CSF and died.