Risk Factors for Hospitalization or Death Among Adults With Advanced HIV at Enrollment for Care in South Africa: A Secondary Analysis of the TB Fast Track Trial

Claire J. Calderwood1,2,8, Mpho Tlali1, Aaron S. Karat1, Christopher J. Hoffmann,4, Salome Charalambous,5,6 Suzanne Johnson,6 Alison D. Grant1,5,7, and Katherine L. Fielding1,8

1Clinical Research Department, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK, 2Institute for Global Health, University College London, London, UK, 3The Aurum Institute, Johannesburg, South Africa, 4Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, 5School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 6Foundation for Professional Development, Pretoria, South Africa, 7Africa Health Research Institute, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa, and 8Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK

Background. Individuals with advanced HIV experience high mortality, especially before and during the first months of antiretroviral therapy (ART). We aimed to identify factors, measurable in routine, primary health clinic–based services, associated with the greatest risk of poor outcome.

Methods. We included all individuals enrolled in the standard-of-care arm of a cluster-randomized trial (TB Fast Track); adults attending participating health clinics with CD4 ≤150 cells/µL and no recent ART were eligible. Associations between baseline exposures and a composite outcome (hospitalization/death) over 6 months were estimated using multivariable Cox regression.

Results. Among 1515 individuals (12 clinics), 56% were female, the median age was 36 years, and the median CD4 count was 70 cells/µL. Within 6 months, 89% started ART. The overall rate of hospitalization/death was 32.5 per 100 person-years (218 outcomes/671 person-years). Lower baseline CD4 count (adjusted hazard ratio [aHR], 2.27 for <50 vs 100–150 cells/µL; 95% CI, 1.57–3.27), lower body mass index (aHR, 2.13 for BMI <17 vs ≥25 kg/m²; 95% CI, 1.31–3.45), presence of tuberculosis-related symptoms (aHR, 1.87 for 3–4 symptoms vs none; 95% CI, 1.20–2.93), detectable urine lipoarabinomannan (aHR, 1.97 for 1+ positivity vs negative; 95% CI, 1.37–2.83), and anemia (aHR, 4.42 for severe anemia [hemoglobin <8 g/dL] vs none; 95% CI, CI 2.38–8.21) were strong independent risk factors for hospitalization/death.

Conclusions. Simple measures that can be routinely assessed in primary health care in resource-limited settings identify individuals with advanced HIV at high risk of poor outcomes; these may guide targeted interventions to improve outcomes.

Keywords. HIV; opportunistic infections; tuberculosis; anemia.

Despite the expansion of access to antiretroviral therapy (ART), many people present to HIV services with advanced disease, particularly in Southern Africa [1]. These individuals experience the greatest burden of morbidity and mortality, particularly due to tuberculosis (TB) and other opportunistic infections (OIs) [2, 3], resulting in high health care costs [4]. However, several trials of empiric TB treatment have failed to demonstrate improved survival. Understanding the pathways leading to poor outcomes may aid development of novel approaches to improve outcomes and facilitate targeted interventions for the highest-risk individuals.

Lower CD4 count and/or advanced World Health Organization (WHO) stage, TB, and other OIs are all commonly described risk factors for death among people with HIV [2, 5–7]; ART improves outcomes [8]. Other risk factors include malnutrition [7], anemia [9, 10], and sociodemographic factors such as male gender [11, 12], older age [13–15], and lower socioeconomic position [16]. These factors have mostly been described among ART-naïve individuals at ART initiation and at large clinics or hospitals. Few studies have included ART-experienced individuals who are re-engaging with care; however, this group represents an increasing proportion of people attending HIV services with advanced disease [5, 10]. While mortality is decreasing among people with severe immunosuppression at ART initiation, likely due to improved clinical care, the first months of ART remain a period of exceptionally high risk of poor outcomes [5, 17].

Understanding and addressing drivers of mortality among people with advanced HIV as early as possible after entering
HIV care is of critical importance in improving overall outcomes among this group [18]. This analysis aimed to identify risk factors, measurable at entry to HIV care among adults with advanced HIV in routine primary health clinics (PHC) in South Africa, for increased rate of the composite outcome of death or hospitalization over the subsequent 6 months and to explore the underlying causal pathways by which these factors contribute to individual outcomes.

METHODS

Study Setting and Design
This analysis drew on data from the TB Fast Track trial; a pragmatic, 2-arm cluster-randomized trial in South Africa, employing a nurse-led risk stratification algorithm to guide empiric TB treatment [19]. To reflect the experience of individuals in routine care, data from the standard-of-care arm of the trial were used [19, 20]. Briefly, adults (aged ≥18 years) with HIV who attended 12 participating clinics in 3 provinces of South Africa (Limpopo, North West, and 2 districts in Gauteng) with available CD4 results were invited to participate. Included individuals were willing to start ART and had a CD4 count of ≤150 cells/µL. Exclusion criteria were recent TB treatment (past 3 months) or ART (past 6 months), contraindication to first-line ART, or being too unwell at the first visit to be managed in primary care (defined in the Supplementary Data). Of 1579 individuals screened (December 2012–December 2015), 1515 individuals (96%) were enrolled [19].

Patient Consent
TB Fast Track received ethical approval from the University of the Witwatersrand, South Africa, and London School of Hygiene & Tropical Medicine, United Kingdom, and informed written consent was obtained from all participants.

Outcome and Exposures of Interest
A composite outcome of hospitalization or death was used. Individuals were censored at the first of either event, the last date known to be alive, or the end of follow-up (6 months). Robust measures were in place to trace individuals regardless of retention in HIV care. Participants were asked to contact the study team in case of hospitalization. Participant or nominated relative (for those who died) interview at 6 months included questions about dates of hospitalization events and death. Data were additionally abstracted from clinical case note reviews at 2 and 6 months and hospital record reviews. Data were linked to vital registration systems for participants with unknown outcomes at 6 months [19].

Exposures of interest were sociodemographic characteristics (age, gender, socioeconomic position), CD4 count, body mass index (BMI), current TB, cryptococcal antigenemia (CrAg), and anemia. BMI and anemia were analyzed as categorical variables, per WHO definitions, to facilitate clinical interpretation of associations (Supplementary Table 1.1 and 1.2) [21, 22]. We considered several measures associated with TB disease: TB-related symptoms (as defined by the WHO symptom screen: fever, weight loss, night sweats, and cough [23]), urine lipoarabinomannan (Determine TB LAM, Alere Inc, Waltham, MA, USA [LAM]; post–January 2014 reference standard), and sputum-based TB tests (Xpert MTB/RIF or acid-fast bacilli smear). LAM was measured retrospectively after study completion for all participants with semiquantitative grading against the post–January 2014 reference standard (unlike the primary trial analysis) [24]; 3+ and 4+ intensity bands were grouped due to data sparsity. Sputum-based TB tests were only performed if required as part of routine care. Hemoglobin was recorded where performed as part of routine care. CD4 count and age were modeled as categorical variables by dividing into thirds or quartiles, respectively, after exploration of the functional form of this association using fractional polynomials. All participants with an adequate dried blood spot sample had blood retrospectively assayed for CrAg. Routine testing was additionally performed as per national guidelines, where a recommendation for CrAg among people with HIV and CD4 <100 cells/µL was introduced while the trial was ongoing. Dates of TB treatment, ART, isoniazid preventative therapy (IPT), and co-trimoxazole preventative therapy (CPT) initiation were recorded. National guidelines advised ART initiation 2–8 weeks after starting TB treatment; same-day ART (for people without TB) was not included in national guidelines [25].

Statistical Analysis
Analyses were conducted using Stata, version 15 (StataCorp, College Station, TX, USA). Cox proportional hazards regression was used to estimate associations between exposures and the outcome. Multivariable models were developed using a forward approach, with age and gender included a priori. Factors were grouped into distal, intermediate, and proximal, with relationships as described in Figure 1. In view of complex relationships between exposures of interest, 2 models were developed. Model A estimated the total effect of each factor of interest, adjusting for distal and intermediate factors. Model B included all identified risk factors to describe direct effects [30]. The Stata code used for each model is provided in the Supplementary Data.

We assessed the proportional hazards assumption and collinearity in both multivariable models. Clinic-level clustering was accommodated using a fixed effect for district (4-level variable). Likelihood ratio tests (LRTs) were conducted for overall association, linear trend, and departures from linearity.

A complete case record approach was employed. There were considerable missing data for hemoglobin, because at 3 clinics ≤25% of participants underwent testing. Analyses of anemia were therefore restricted to 9 clinics with routine hemoglobin
A socioeconomic position score was generated using principal component analysis; the score was grouped into quintiles (Supplementary Table 1.3). Population-attributable fractions (PAFs) were calculated using estimates from multivariable models [31].

The diagnostic tests available in TB Fast Track may not be available in routine clinical care. As a sensitivity analysis, we explored the impact of including these tests in our model, repeating the analysis considering only clinical factors.

RESULTS

Study Population

A total of 1515 participants across 12 clinics were included, with few missing data aside from hemoglobin (29% missing overall, 7% when restricted to 9 clinics) (Table 1). Fifty-six percent (849/1515) of participants were female, the median age (interquartile range [IQR]) was 36 (18–83) years, and the median CD4 count (IQR) was 70 (35–113) cells/µL.

At enrollment, 65% (992/1511) of participants reported at least 1 TB-related symptom: 59% had weight loss, 33% cough, 20% night sweats, 16% fever. TB tests were performed in 250 participants at enrollment or in the following 2 weeks; 31/250 (12%) had evidence of TB (Figure 2).

Urine LAM (performed after study completion) was detectable in 15% of participants (222/1463 with an adequate sample), with 4% (60/1463) positive at the 2+ level. Less than 1% of participants were CrAg positive (11/1410 with an adequate sample). Forty-seven percent (716/1514) were taking CPT and 10% (158/1514) IPT at enrollment, with initiation at a median (IQR) interval of 2 (–10 to 0) days or 1 (–10 to 0) day before enrollment, respectively.

Over 6 months, 89% of participants started ART and 12% of participants started TB treatment. The median interval from...
| Table 1. Distribution of Sociodemographic Factors at Baseline and Rates and Univariable Hazard Ratios for Time to Hospitalization/Death (n = 1515) |
|---------------------------------------------------------------|
| **Sex (n = 1515)**                                            |
| Female                                                       | 849 (56) | 113380 | 29.8 | Ref |
| Male                                                        | 666 (44) | 105292 | 36.0 | 1.22 (0.93–1.60) |
| **Age, y (n = 1515)**                                        |
| 18–29                                                       | 290 (19) | 33130 | 25.29 | .2 |
| ≥45                                                        | 315 (21) | 43141 | 30.42 | 1.21 (0.77–1.90) |
| **Country of origin (n = 1514)**                             |
| South Africa                                                | 1373 (91) | 201610 | 32.9 | Ref |
| Other SSA                                                   | 141 (9) | 1761 | 28.1 | 0.85 (0.51–1.41) |
| **SEP quintile (n = 1489)**                                  |
| 1 (lowest)                                                  | 298 (20) | 44131 | 33.6 | Ref |
| 2                                                         | 298 (20) | 37133 | 27.9 | 0.84 (0.54–1.30) |
| 3                                                          | 298 (20) | 44132 | 33.4 | 1.00 (0.66–1.53) |
| 4                                                          | 298 (20) | 48132 | 36.3 | 1.11 (0.73–1.67) |
| 5 (highest)                                                 | 297 (20) | 40132 | 30.3 | 0.94 (0.60–1.47) |
| **CD4 count, cells/µL (n = 1515)**                          |
| <50                                                        | 522 (34) | 113217 | 52.1 | 2.63 (1.86–3.72) |
| >100                                                      | 497 (33) | 45233 | 19.3 | Ref |
| **BMI, kg/m² (n = 1512)**                                   |
| <17                                                       | 141 (9) | 3658 | 62.4 | 2.89 (1.81–4.59) |
| >17–18.4                                                  | 130 (9) | 2256 | 39.5 | 1.84 (1.06–3.13) |
| 18.5–24.9                                                  | 872 (58) | 122386 | 31.6 | 1.47 (1.01–2.12) |
| **TB-related symptoms (n = 1511)**                          |
| None                                                      | 518 (34) | 50242 | 20.7 | Ref |
| 1                                                          | 491 (33) | 61220 | 27.8 | 1.35 (0.92–1.98) |
| 2                                                          | 302 (20) | 66124 | 53.1 | 2.55 (1.76–3.71) |
| 3                                                          | 200 (13) | 4184 | 49.0 | 2.42 (1.59–3.70) |
| **TB tests performed (n = 1515)**                           |
| None                                                      | 1265 (84) | 184561 | 32.8 | Ref |
| 1                                                        | 195 (13) | 2189 | 23.7 | 0.71 (0.45–1.13) |
| 2                                                        | 31 (2) | 713 | 55.9 | 1.68 (0.79–3.59) |
| Unkown                                                    | 24 (2) | 69 | 65.0 | 1.86 (0.82–4.19) |
| **Previous TB treatment (n = 1515)**                        |
| No                                                       | 1379 (91) | 196611 | 32.1 | Ref |
| Yes                                                      | 136 (9) | 2260 | 36.7 | 1.15 (0.74–1.78) |
| **Previous TB test (<6 mo) (n = 1515)**                     |
| No                                                       | 873 (58) | 118390 | 30.2 | Ref |
| Yes                                                      | 642 (42) | 100281 | 35.6 | 1.13 (0.90–1.55) |
| **LAM (n = 1463)**                                         |
| Negative                                                  | 1241 (85) | 146565 | 25.9 | Ref |
| 1                                                        | 162 (11) | 3865 | 58.6 | 2.22 (1.55–3.17) |
| 2                                                        | 31 (2) | 1111 | 98.2 | 3.71 (2.01–6.87) |
| 3                                                        | 29 (2) | 139 | 150.6 | 5.56 (3.14–9.84) |
| **Serum CrAg (n = 1410)**                                  |
| Negative                                                  | 1399 (99) | 207618 | 29.5 | Ref |
| Positive                                                  | 11 (1) | 15 | 20.2 | 0.62 (0.09–4.43) |
| **Current CPT (n = 1514)**                                 |
| No                                                       | 798 (53) | 106355 | 29.9 | Ref |
| Yes                                                      | 716 (47) | 112316 | 35.5 | 1.19 (0.89–1.57) |
| **Current IPT (n = 1514)**                                 |
| No                                                       | 1356 (90) | 197598 | 33.0 | Ref |
| Yes                                                      | 158 (10) | 2173 | 28.9 | 0.86 (0.54–1.37) |
| **Restricted data set (9 clinics)**                        |
| Anemia (n = 1021/1099)                                     |
| Severe                                                   | 94 (9) | 2836 | 77.1 | 4.86 (2.73–8.66) |
| Moderate                                                 | 380 (37) | 64166 | 38.6 | 2.52 (1.52–4.17) |
| Mild                                                     | 260 (26) | 37116 | 31.9 | 2.07 (1.20–3.58) |

Anemia was categorized according to WHO definitions (severe anemia = Hb < 80 g/dL; moderate anemia = Hb ≥ 80 and < 110 g/dL; mild anemia = Hb ≥ 110 and < 130 [if male] or < 120 [if female]); none = Hb ≥ 130 [if male] or ≥ 120 [if female]).

Abbreviations: BMI, body mass index; CPT, co-trimoxazole preventative therapy; CrAg, cryptococcal antigen; Hb, hemoglobin; HR, unadjusted hazard ratio; IPT, isoniazid preventative therapy; LAM, urine lipoarabinomannan; LRT, likelihood ratio test; n, number of individuals with nonmissing data for this variable; ref, reference category; P, P value from likelihood ratio test for association; PY, person-years at risk; SEP, socioeconomic position; SSA, Sub-Saharan Africa; TB, tuberculosis; WHO, World Health Organization.

HR from Cox regression model adjusted for clustering using fixed effect for district.

bP < .001 from LRT for linear association; no evidence for departure from linearity (P > .3) apart from for number of TB-related symptoms where P = .09.

cThese were either sputum acid-fast bacilli smear or Xpert MTB/RIF within 0–14 days after study enrollment.

These were either sputum acid-fast bacilli smear or Xpert MTB/RIF within 0–14 days after study enrollment.

Anemia analyses use a restricted data set as described in text. Overall, 1080/1515 individuals had hemoglobin measured.
enrollment to ART (IQR) was 11 (5–21) days, and the median interval (IQR) to starting TB treatment was 6 (1–17.5) days. The interval between enrollment and ART was longer among those who also started TB treatment compared with those who did not (median [IQR], 29 [15–55] and 9 [4–19] days, respectively). Ninety-seven percent (1258/1297) of those who did not experience the outcome completed at least 5 months of follow-up. The overall mortality rate was 24.4 per 100 person-years (95% CI, 17.3–34.6).

Rate of Hospitalization or Death
Two hundred eighteen individuals were hospitalized or died over 671 person-years of follow-up (comprising 60 deaths and 158 hospitalizations; 91 individuals censored at hospitalization died within 6 months of enrollment). The overall rate of hospitalization/death was 32.5 per 100 person-years; 66.0 per 100 person-years before and 22.5 per 100 person-years after initiation of ART (95% CI, 1.86–3.82; aHR, 3.25; 95% CI, 1.34–1.97; per 50 cell/µL category decrease).

Risk Factors for Hospitalization or Death
Univariable analyses showed little evidence for associations between sociodemographic measures and rate of hospitalization/death (Table 1). Strong evidence for univariable associations between each of CD4 count, BMI, TB-related symptoms, detectable urine LAM, and anemia was observed (Table 1; Supplementary Figure 1).

In multivariable analyses, lower CD4 count, lower BMI, presence of TB-related symptoms, detectable LAM, and more severe anemia were strong risk factors for shorter time to hospitalization/death (Table 2). After adjustment for sex, age, and district (model A), lower CD4 count was strongly associated with increased rate of hospitalization/death, with 2.7 times the hazard in those with CD4 <50 cells/µL compared with those with CD4 100–150 cells/µL (95% CI, 1.86–3.82; aHR, 2.66; 95% CI, 1.34–1.97; per 50 cell/µL category decrease).

Lower BMI was strongly associated with shorter time to outcome after adjustment for CD4 count, sex, age, and district (model A): Those who were moderately to severely underweight (BMI <17 kg/m²) experienced over twice the rate of hospitalization/death compared with those in the highest BMI category (BMI ≥25 kg/m²; aHR, 2.66; 95% CI, 1.34–3.25).

Individuals with TB-related symptoms had a higher rate of hospitalization/death compared with those without, with greater hazard for each additional symptom reported. Individuals with 3 or more symptoms experienced over double the rate of these outcomes compared with those with none (aHR, 3.25; 95% CI, 1.34–3.25).

LAM positivity at 1+ intensity band was associated with a doubling in hazard compared with a negative result (HR, 2.05; 95% CI, 1.43–2.95), with a graded association across increasing levels of positivity (aHR, 1.72 per category increase from 1+ to 3–4+; 95% CI, 1.46–2.02).

In model B, all potential risk factors identified were included, irrespective of proposed mediating pathways. This demonstrated strong evidence for independent associations for each of CD4, BMI, LAM, and number of TB-related symptoms with Advanced HIV and Hospitalization/Death • OFID • 5
the outcome. The effect size associated with the lowest CD4 counts (<50 cells/µL) was slightly smaller than observed in model A, suggesting mediation of the effect of CD4 count through lower BMI and/or markers of TB disease and OI. Similarly, when adjusted for TB-related symptoms, TB tests, and LAM, the magnitude of the hazard associated with being severely underweight (BMI <17 kg/m²) was smaller. When only clinical factors were considered, findings were similar (Supplementary Table 2.1).

In the data set restricted to 9 clinics for which hemoglobin data were available, anemia was strongly associated with increased rate of hospitalization/death after adjustment for sex, age, CD4 count, BMI, LAM, TB-related symptoms, and district. Those with severe anemia had over 4 times the hazard of hospitalization/death compared with none, with an aHR of 1.55 (95% CI, 1.27–1.89) per category increase in severity.

There was evidence for violation of the proportional hazards assumption in the association of baseline CD4 count with the outcome, with the increased hazard associated with lower CD4 count at study enrollment lessening over time (P = .03) (Table 3). For other risk factors considered, the proportional hazards assumption was met.

### Population-Attributable Fractions

PAFs were calculated assuming independent causal associations with the outcome and adjusted for all other potential risk factors (Table 2). CD4 count <100 cells/µL and presence of anemia appeared to have the greatest population impact.
on rates of hospitalization/death (PAF 38% and 48%, respectively; 95% CI, 20%–53% and 34%–80%).

DISCUSSION

Adults with advanced HIV in South Africa are at very high risk of hospitalization or death within 6 months of enrolling in care, particularly in the period before ART initiation. Within this population, clinical assessments and simple tests were strong risk factors for adverse outcomes, with independent associations between each of anemia, lower CD4 count, lower BMI, detectable urine LAM, presence of TB-related symptoms, and hospitalization/death. The greatest effect size was seen with positive LAM and anemia, but the greatest population impact could be attributed to lower CD4 count and anemia, reflecting the high prevalence of these factors among the study population.

Identification and management of people with advanced HIV remain critically important to improving individual outcomes. Despite rollout of earlier ART initiation, presentation with advanced disease remains common in South Africa [32]. Current recommendations for differentiated care for people with advanced HIV disease include prioritization for rapid initiation on ART. However, TB-related symptoms are common, often leading to a delay in ART [33]. Such delays may underlie the lack of benefit demonstrated by empiric TB treatment trials among people with advanced HIV, such as TB Fast Track [19]. Same-day ART initiation, despite TB-related symptoms, may improve outcomes by reducing the “pre-ART” period; however, evidence for specific approaches which facilitate this is currently lacking [34].

Rates of adverse outcomes among people with advanced HIV are not fully mitigated by ART initiation or explained by lower CD4 count. This, together with identification of BMI, anemia, LAM, and TB-related symptoms as risk factors for hospitalization/death, suggest that other strategies that directly address these risks may offer additional benefit. Such strategies may include rifamycin-containing TB-preventative therapy [35] and enhanced antimicrobial prophylaxis [36].

The pathways toward adverse outcomes among people with advanced HIV are, however, complex and interdependent. Such mediation is illustrated in our analysis by smaller direct effects (model B) as compared with total effects (model A) for all factors considered. This may suggest that a strategy targeting a single pathway may be insufficient and that further development and evaluation of multicomponent interventions, including both medical and nonmedical (eg, adherence counseling, financial support) elements, are required.

In this analysis, there was no association between IPT and CPT and hospitalization/death, despite clear evidence of reduced mortality with these strategies from randomized controlled trials [27]. The apparent lack of benefit may reflect low coverage, with fewer than half of participants taking CPT and only 10% IPT at enrollment, or insufficient duration of therapy, with most of those who were taking CPT/IPT starting around the time of enrollment, but the majority of adverse outcomes occurring early in follow-up. Finally, this finding may also reflect misclassification of exposure as data on CPT/IPT initiation after enrollment are not available.

In our study, simple tests (LAM, CD4, and hemoglobin) identified the people at highest risk of poor outcomes, with larger effect sizes and population-attributable fractions compared with clinical factors. LAM for TB diagnosis among people with HIV was not in routine use at the time of this study; however, 14% of outpatients with advanced HIV had detectable LAM, and +1 LAM positivity was associated with double the rate of hospitalization/death compared with a negative result. This further supports the systematic use of LAM in outpatient HIV care [37]. Measurement of CD4 is becoming less common in the era of test-and-treat; however, we suggest that it may continue to have a role in guiding differentiated care.

Despite commercially available cheap, battery-powered, or lateral flow point-of-care assays, tests for anemia or LAM are frequently not available in routine care. Improving access to such diagnostics may improve outcomes by promoting individualized care, enabling specific interventions to be tailored toward those most likely to benefit, or identifying people who require closer clinical monitoring or increased adherence or social support. Evaluation of diagnostics should be included in interventional studies for advanced HIV, particularly in the context of recent trials, which have not demonstrated

| Duration of Follow-up | Overall (N = 207) | Month 1 (n = 90) | Month 2–3 (n = 71) | Month 4–6 (n = 48) |
|-----------------------|------------------|------------------|-------------------|------------------|
| Baseline CD4 Count, cells/µL | aHR (95% CI) | aHR (95% CI) | aHR (95% CI) | aHR (95% CI) |
| <50 | 2.66 (1.86–3.82) | 5.47 (2.69–11.2) | 2.10 (1.19–3.71) | 1.64 (0.85–3.17) |
| 50–99 | 1.51 (1.02–2.25) | 3.75 (1.79–7.87) | 1.05 (0.57–2.09) | 0.66 (0.29–1.50) |
| 100–150 | Ref | Ref | Ref | Ref |

Pinteraction = .02. Hazard ratios were adjusted for age, sex, and district presented (ie, model A above). In a model adjusted for age, sex, body mass index, number of tuberculosis symptoms, urine lipoarabinomannan, and district (ie, model B above), a similar association was observed (Pinteraction = .02).

Abbreviations: aHR, adjusted hazard ratio; n = number of outcomes observed in the time period indicated.
benefit of interventions when applied to all “advanced HIV” [38, 39].

Many people with TB-related symptoms did not start TB treatment. This may reflect low specificity of symptom screening, but missed TB diagnoses due to limited availability and sensitivity of diagnostic tests are common, and better access to diagnostics (including routine use of LAM) may be important [40, 41]. Eighty-seven percent of people reporting TB-related symptoms had not had a sputum-based TB test 2 weeks later, perhaps suggesting lack of routine symptom-based TB screening, nondisclosure of symptoms to clinic staff, or positive symptom screens not being acted on, for example, due to difficulties accessing tests. It is possible that participants had TB tests and/or treatment initiation at a nonstudy health facility that were not captured. Both TB and other OIs cause TB-related symptoms. In a TB Fast Track substudy, 34 participants who died had minimally invasive autopsy: 47% had evidence of TB disease, 38% of those had not been on TB treatment, and multiple infections were common, mostly TB and bacterial infection [3].

The identified risk factors are generally consistent with those from other studies, though some findings differ [17]. Two systematic reviews concluded that men initiated on ART in Africa have higher mortality than women; no association was seen here [11, 12]. Univariable point estimates suggested increased hazard of hospitalization/death among men, though evidence was weak, and this was not seen after adjustment for more proximate factors, suggesting no direct effect. A number of studies included in the meta-analyses did not adjust for such confounding. Socioeconomic differences have been described as risk factors for HIV mortality [16]. Here, no trend was observed, perhaps reflecting a relatively homogenous, economically disadvantaged population. The data used in our analysis included data collected before ART initiation, which may also account for some of the differences compared with previous work.

The strengths of this analysis include the large sample size, few missing data, and complete follow-up, including for individuals not retained in care. Careful consideration of causal pathways facilitated estimation of total and direct effects of each risk factor and adjustment for confounding. TB Fast Track had few exclusion criteria; was based in PHCs; included individuals at receipt of CD4 results, not ART initiation; and, unlike most previous studies, was not restricted to ART-naïve individuals. This reflects real-world experience. We did, however, restrict to CD4 ≤150 cells/µL, rather than the standard definition of advanced HIV (200 cells/µL), and therefore cannot conclude that identified risk factors apply to less severe immunosuppression.

An important consideration when interpreting these findings is that individuals must not have received TB treatment in the previous 3 months to be enrolled, but 42% reported a TB test in the past 6 months. This was higher than expected and may be attributable to Xpert rollout during the study period. Aside from misclassification, recall, and social desirability bias, it must be assumed that these tests were negative. This exclusion is likely to have led to artificially low rates of TB disease; however, data from the autopsy sub-study suggest similar TB prevalence among those who died to that found in other studies from the region [3, 42]. Individuals who did not attend to receive their CD4 result were not included in the study; it is likely that a significant number of this group did not start ART and therefore they may have been at higher risk of poor outcomes or may have had a different profile of risk factors.

As we considered only baseline risk factors, another limitation is potential time-dependent confounding: this may underestimate the violation of proportional hazards observed in the case of CD4 count. CD4 counts may change rapidly, particularly when ART is initiated. As a result, an individual’s CD4 count at the time they experienced the outcome may be different from baseline.

In keeping with the pragmatic design of the trial, a limited number of variables were recorded, with possible resultant unmeasured confounding. In estimation of PAFs, we assumed a causal link between risk factors and the outcome; however, it is important to recognize in interpretation of these estimates that the effects of the factors described are mediated through other pathways such as infections and inflammatory changes, and they are not direct causes of the outcomes described. Further, residual or unmeasured confounding in these observational data is possible. Given the limited number of clusters, we did not attempt to evaluate clinic-level factors, which may also be important.

A composite outcome was selected to increase study power. Given very high mortality among hospitalized patients with advanced HIV, we proposed that hospitalization and death are both clinically important and that risk factors are likely to be similar for both [43]. Three-quarters of participants experiencing the outcome were censored at hospitalization: use of a composite outcome may have obscured factors associated with death but not hospitalization. However, 29% of hospitalized individuals died within 10 days of this event, suggesting that hospitalization is a relevant measure of severe morbidity.

CONCLUSIONS

Individuals entering HIV care with advanced disease in South Africa have high morbidity and mortality. Here, clinical measures that may be routinely assessed in decentralized HIV services were identified as risk factors for the worst outcomes among this already high-risk group. As well as highlighting the ongoing need for earlier HIV diagnosis and ART to avoid
advanced disease, this analysis suggests that simple clinical measures may enable differentiated care for individuals at the highest risk and therefore reduce the unacceptably high mortality in this group.

**Supplementary Data**

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

**Acknowledgments**

We gratefully acknowledge the contribution of our study participants, the work of the study team, and the cooperation of Department of Health staff in participating clinics for the TB Fast Track study. **Financial support.** The TB Fast Track study was funded by Joint Global Health Trials (UK Medical Research Council, UK Department for International Development, Wellcome Trust, as part of the EDCTP2 programme supported by the European Union; G1100689) and the Bill & Melinda Gates Foundation (OPP1083118). Alere donated materials for quality control of their lipoarabinomannan assay.

**Potential conflicts of interest.** All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Author contributions.** A.D.G., S.C., C.J.H., S.J., and K.L.F. conceived, designed, and secured funding for the TB Fast Track study. A.D.G., S.C., M.T., A.S.K., S.J., and K.L.F. were responsible for data collection. C.J.C. analyzed the data and drafted the manuscript. All authors contributed to data interpretation and critically reviewed the manuscript.

**References**

1. Osler M, Hilderbrand K, Goemaere E, et al. The continuing burden of advanced HIV disease over 10 years of increasing antiretroviral therapy coverage in South Africa. Clin Infect Dis 2018; 66:S118–25.
2. Gupta A, Nadkarni G, Yang WT, et al. Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): a systematic review and meta-analysis. PLoS One 2011; 6:e28693.
3. Karat AS, Omar T, von Gottberg A, et al. Autopsy prevalency of tuberculosis and other potentially treatable infections among adults with advanced HIV enrolled in out-patient care in South Africa. PLoS One 2016; 11:e0166158.
4. Fleishman JA, Yehia BR, Moore RD, Gebo KA. The economic burden of late entry into medical care for patients with HIV infection. Med Care 2010; 48: 1071–9.
5. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in Sub-Saharan Africa. AIDS 2008; 22:1897–908.
6. Strayemanns M, Bierenbach AL, Nagelkerke N, Glaziov P, van der Werf MJ. The effect of tuberculosis on mortality in HIV positive people: a meta-analysis. PLoS One 2010; 5:e15241.
7. Komati S, Shaw PA, Stubbs N, et al. Tuberculosis risk factors and mortality for HIV-infected persons receiving antiretroviral therapy in South Africa. AIDS 2010; 24:1849–55.
8. TEMPRANO ANRS Study Group, Daniel C, Mok R, et al. A trial of early antituberculosis and isoniazid preventive therapy in South Africa. N Engl J Med 2015; 373: 808–22.
9. Russell EC, Charalambous S, Pamba L, et al. Low haemoglobin predicts early mortality among adults starting antiretroviral therapy in an HIV care programme in South Africa: a cohort study. BMC Public Health 2010; 10:433.
10. Kerkhoff AD, Wood R, Cobelens FG, Gupta-Wright A, Bekker LG, Lawn SD. The predictive value of current haemoglobin levels for incident tuberculosis and/or mortality during long-term antiretroviral therapy in South Africa: a cohort study. BMC Med 2015; 13:70.
11. Duysts E, Dybul M, Kanters S, et al. Male sex and the risk of mortality among individuals enrolled in antiretroviral therapy programs in Africa: a systematic review and meta-analysis. AIDS 2013; 27:417–25.
12. Beckham SW, Beyeir C, Luckow P, Doherty M, Negussie EK, Baral SD. Marked sex differences in all-cause mortality on antiretroviral therapy in low- and middle-income countries: a systematic review and meta-analysis. J Int AIDS Soc 2016; 19:21106.
13. Mutvedzi PC, Lessells RJ, Rodger AJ, Newell ML. Association of age with mortality and virological and immunological response to antiretroviral therapy in rural South African adults. PLoS One 2011; 6:e21795.
14. Maskew M, Brennan AT, Westreich D, McNamara L, MacPhail AP, Fox MP. Gender differences in mortality and CD4 count response among virally suppressed HIV-positive patients. J Womens Health 2013; 22:113–20.
15. Dawood H, Hassan-Moosa R, Zuma NY, Naidoo K. Mortality and treatment response amongst HIV-infected patients 50 years and older accessing antiretroviral services in South Africa. BMC Infect Dis 2018; 18:168.
16. Probst C, Parry CD, Rehm J. Socio-economic differences in HIV/AIDS mortality in South Africa. Trop Med Int Heal 2016; 21:846–55.
17. Ayalew MR. Mortality and its predictors among HIV infected patients taking antiretroviral treatment in Ethiopia: a systematic review. AIDS Res Treat 2017; 2017: 5415298.
18. Sempijja V, Namulume A, Ankunda R, et al. Temporal trends of early mortality and its risk factors in HIV-infected adults initiating antiretroviral therapy in Uganda. EClinicalMedicine 2020; 28:100600.
19. Grant AD, Charalambous S, Thali M, et al. Algorithm-guided empirical tuberculosis treatment for people with advanced HIV (TB Fast Track): an open-label, cluster-randomised trial. Lancet HIV 2020; 7:e27–37.
20. Fielding KL, Charalambous S, Hoffmann CJ, et al. Evaluation of a point-of-care tuberculosis test-and-treat algorithm on early mortality in people with HIV accessing antiretroviral therapy (TB Fast Track study): study protocol for a cluster randomised controlled trial. Trials 2015; 16:125.
21. World Health Organization. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severe. World Health Organization; 2011.
22. World Health Organization. Obesity: Preventing and Managing the Global Epidemic (Report of a WHO Consultation). World Health Organization; 2000.
23. Getahun H, Kitiikraisk W, Heilig CM, et al. Development of a standardized screening tool for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. PLoS Med 2011; 8:e1000391.
24. Thali M, Fielding KL, Karat AS, et al. Sensitivity of the lateral flow urine lipoarabinomannan assay in ambulant adults with advanced HIV disease: data from the TB Fast Track study. Trans R Soc Trop Med Hyg 2020; 114:556–60.
25. National Department of Health South Africa. Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents. National Department of Health South Africa, 2010.
26. Cegelski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis 2004; 8:286–98.
27. Bade J, Moh R, Gabillard D, et al. Effect of isoniazid preventive therapy on risk of death in West African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. Lancet Glob Heal 2017; 5: e1080–89.
28. World Health Organization. Consolidated Guidelines on the Use of Anti-Retroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. World Health Organization; 2016.
29. Suthar AB, Vitoria MA, Nagata JM, et al. Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. Lancet HIV 2015; 2:e137–50.
30. Westreich D, Greenland S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. Am J Epidemiol 2013; 177:292–8.
31. Newson RB. Attributable and unattributable risks and fractions and other scenarios comparisons. Stata J 2013; 188:1659–724.
32. Garmona S, Bor J, Nattey C, et al. Persistent high burden of advanced HIV disease among patients seeking care in South Africa’s national HIV program: data from a nationwide laboratory cohort. Clin Infect Dis 2018; 66:3111–7.
33. World Health Organization. Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy. World Health Organization; 2017.
34. Burke RM, Rickman HM, Singh V, et al. Same-day antiretroviral therapy initiation for people living with HIV who have tuberculosis symptoms: a systematic review. HIV Med 2022; 23:4–15.
35. Yanes-Lane M, Ortiz-Brizuela E, Campbell JR, et al. Tuberculosis preventive therapy for people living with HIV: a systematic review and network meta-analysis. PLoS Med 2021; 18:1–23.
36. Hakim J, Musiime V, Szubert AJ, et al. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. N Engl J Med 2017; 377:233–45.

37. World Health Organization. Lateral Flow Urine Lipoarabinomannan Assay (LF-LAM) for the Diagnosis of Active Tuberculosis in People Living With HIV: Policy Update. World Health Organization; 2019.

38. Mallewa J, Szubert AJ, Mugyenyi P, et al. Effect of ready-to-use supplementary food on mortality in severely immunocompromised HIV-infected individuals in Africa initiating antiretroviral therapy (REALITY): an open-label, parallel-group, randomised controlled trial. Lancet HIV 2018; 5:e231–40.

39. 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.

40. Hamada Y, Lujan J, Schenkel K, Ford N, Getahun H. Sensitivity and specificity of WHO’s recommended four-symptom screening rule for tuberculosis in people living with HIV: a systematic review and meta-analysis. Lancet HIV 2018; 5:e515–23.

41. Gupta-Wright A, Corbett EL, van Oosterhout JJ, et al. Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial. Lancet 2018; 392:292–301.

42. Gupta RK, Lucas SR, Fielding KI, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS 2015; 29:1987–2002.

43. Ford N, Shubber Z, Meintjes G, et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. Lancet HIV 2015; 2:e438–44.