

# HIV Infection as Risk Factor for Death among Hospitalized Persons with Candidemia, South Africa, 2012–2017

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## Learning Objectives

Upon completion of this activity, participants will be able to:

Describe the effect of HIV infection and other factors on mortality risk from candidemia, according to an analysis of data from a 6-year sentinel surveillance study in South Africa

Determine the association of intensive care unit admission with mortality risk among adults with HIV infection and candidemia, according to an analysis of data from a 6-year sentinel surveillance study in South Africa

Identify clinical implications of the effect of HIV infection on mortality risk from candidemia, according to an analysis of data from a 6-year sentinel surveillance study in South Africa

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We determined the effect of HIV infection on deaths among persons  $\geq 18$  months of age with culture-confirmed candidemia at 29 sentinel hospitals in South Africa during 2012–2017. Of 1,040 case-patients with documented HIV status and in-hospital survival data, 426 (41%) were HIV-seropositive. The in-hospital case-fatality rate was 54% (228/426) for HIV-seropositive participants and 37% (230/614) for HIV-seronegative participants (crude odds ratio [OR] 1.92, 95% CI 1.50–2.47;  $p < 0.001$ ). After adjusting for relevant confounders ( $n = 907$ ), mortality rates were 1.89 (95% CI 1.38–2.60) times higher among HIV-seropositive participants than HIV-seronegative participants ( $p < 0.001$ ). Compared with HIV-seronegative persons, the stratum-specific adjusted mortality OR was higher among HIV-seropositive persons not managed in intensive care units (OR 2.27, 95% CI 1.47–3.52;  $p < 0.001$ ) than among persons who were (OR 1.56, 95% CI 1.00–2.43;  $p = 0.05$ ). Outcomes among HIV-seropositive persons with candidemia might be improved with intensive care.

*Candida* is a common cause of healthcare-associated bloodstream infections in South Africa; the estimated national incidence risk in 2016–2017 was 84 (95% CI 81–86) cases per 100,000 hospital admissions (1). This rate is  $\approx 10$ -fold higher than that reported in the United States (2). The death rate among patients with *Candida* bloodstream infections is high and associated with such factors as confirmed or presumed gastrointestinal source of infection, lack of source control, shorter time to positivity of blood cultures, inappropriate or delayed empiric antifungal treatment, lack of consultation with an infectious disease physician, severe sepsis or septic shock, and severity of underlying conditions (3–5). The crude mortality rate associated with candidemia was 43% in South Africa in 2016–2017 (1). In 2 small case series of HIV-seropositive patients with candidemia (Spain,  $n = 37$ ; Italy,  $n = 38$ ), the crude mortality rate was  $\approx 60\%$  (6,7). HIV infection may be a risk factor for death among persons with culture-confirmed candidemia. In a 2014 population-based surveillance study in Spain, 16 (2%) of 752 patients with candidemia were HIV-seropositive (8). Although HIV infection was not associated with death on univariable analysis (OR 0.51, 95% CI 0.07–3.93), the study was underpowered. In contrast, in a United States cohort study of 446 adults with candidemia, 22 (5%) were HIV-seropositive, and HIV infection was associated with a 2-fold increased adjusted hazard of 30-day mortality (hazard ratio 2.02, 95% CI 1.11–3.72) (9). This effect of HIV infection on death rates may be mediated by factors related to the host (e.g., neutropenia or neutrophil dysfunction in persons with advanced HIV

disease) or the fungal pathogen (infection caused by *Candida* species other than *C. albicans* or by  $>1$  *Candida* spp.) (6,7,10–12). Such an association has not been described in a high HIV prevalence setting. By using data from a 6-year sentinel surveillance study at hospitals in South Africa, we examined the effect of HIV infection on the risk for 30-day mortality among persons with candidemia.

## Materials and Methods

### Study Population

We included persons  $\geq 18$  months of age with an episode of culture-confirmed candidemia identified at 29 sentinel hospitals in South Africa during January 1, 2012–December 31, 2017. The HIV prevalence among inpatients is high at these large urban tertiary-academic or regional acute-care hospitals (e.g., 60% at a Cape Town district hospital in 2012–2013) (13). A case was defined as illness in a person in whom *Candida* spp. was cultured from blood at a laboratory providing diagnostic pathology services to a sentinel hospital. An episode was defined as a 30-day period from the date of the first positive *Candida* culture. Any positive blood cultures after this period defined a recurrent episode and thus a new case. We excluded children  $< 18$  months of age because we did not have HIV PCR results to confirm an HIV diagnosis for a sufficient number of persons.

### Surveillance Methods

Cases were reported from public-sector and private-sector pathology laboratories. In general, blood cultures were collected if patients had clinical features of sepsis, including tachycardia, tachypnea, increased or subnormal temperature, a change in sensorium, hypotension, or prostration (14). Viable *Candida* isolates were submitted to a reference laboratory for species-level identification and antifungal susceptibility testing, as previously described (1). Trained nurses or pharmacists identified culture-confirmed cases in the laboratory and interviewed prospectively enrolled participants or their next of kin or reviewed medical charts or electronic laboratory records. Data were collected through a standardized case report form. The main explanatory variable was the participant's HIV infection status, which was determined during the admission for candidemia. HIV status was self-reported during participant interviews or abstracted from the inpatient chart, a child's outpatient immunization card, or laboratory records. An in-hospital outcome with a date of outcome was determined at the end of admission to the acute-care hospital or if

the participant was transferred to a step-down facility; this outcome was determined at the end of that admission. Outcome was recorded as alive at 30 days for prolonged admissions of >30 days after first positive blood culture. Underlying or immediate cause of death was not recorded. Surveillance officers recorded whether a person had been admitted to the intensive care unit (ICU) at any time during hospitalization, but the specific reason for and dates of ICU admission or discharge were not captured. We calculated a quick Pitt score, an abbreviated version of the Pitt bacteremia score, as the sum of individual scores for body temperature of  $<35^{\circ}\text{C}$  (1 point), systolic blood pressure of  $<90$  mm Hg (1 point), cardiac arrest (1 point), mechanical ventilation (1 point), and altered mental status (1 point) on the day of candidemia diagnosis (15,16).

### Data Analysis

We used participant identifiers to remove duplicate records. We described the characteristics of the study participants by using descriptive statistics. To determine risk factors for death, we used classical Mantel-Haenszel methods to calculate crude case fatality ratio, odds ratio (OR), and 95% CI for HIV status and each of the potential confounders (Appendix, <https://wwwnc.cdc.gov/EID/article/27/5/21-0128-App1.pdf>). We did not assume that individual participant-level outcomes were statistically independent in this sentinel surveillance study. We therefore used a random-effects logistic regression analysis to explicitly model between-cluster variation at sentinel sites and simultaneously adjust for participant-level confounders (17) (Appendix). We treated the follow-up period as a fixed 30-day period. We also explored the dose-response effect of HIV on death rates. For this analysis, participants' HIV infection status was recoded as an ordinal variable: HIV-seronegative, HIV-seropositive without advanced immunosuppression (CD4 count  $\geq 200$  cells/ $\mu\text{L}$ ), and HIV-seropositive with advanced immunosuppression (CD4 count  $<200$  cells/ $\mu\text{L}$ ). Before conducting the analysis, we hypothesized that the effect of HIV infection on death rates would differ among participants with candidemia managed in an ICU and those who were not admitted to an ICU; therefore, we considered ICU admission as an effect modifier a priori. We included participants with recorded dates of positive *Candida* specimen collection and 30-day outcome in a Kaplan-Meier survival analysis. For 67 participants with an outcome date that coincided exactly with the specimen collection date, we recoded their time-to-outcome to 0.5 days. We explored the association

between HIV status and ICU admission by classical and multivariable random effects logistic regression analyses as a post-hoc analysis to explore reasons for the main results.

### Ethics

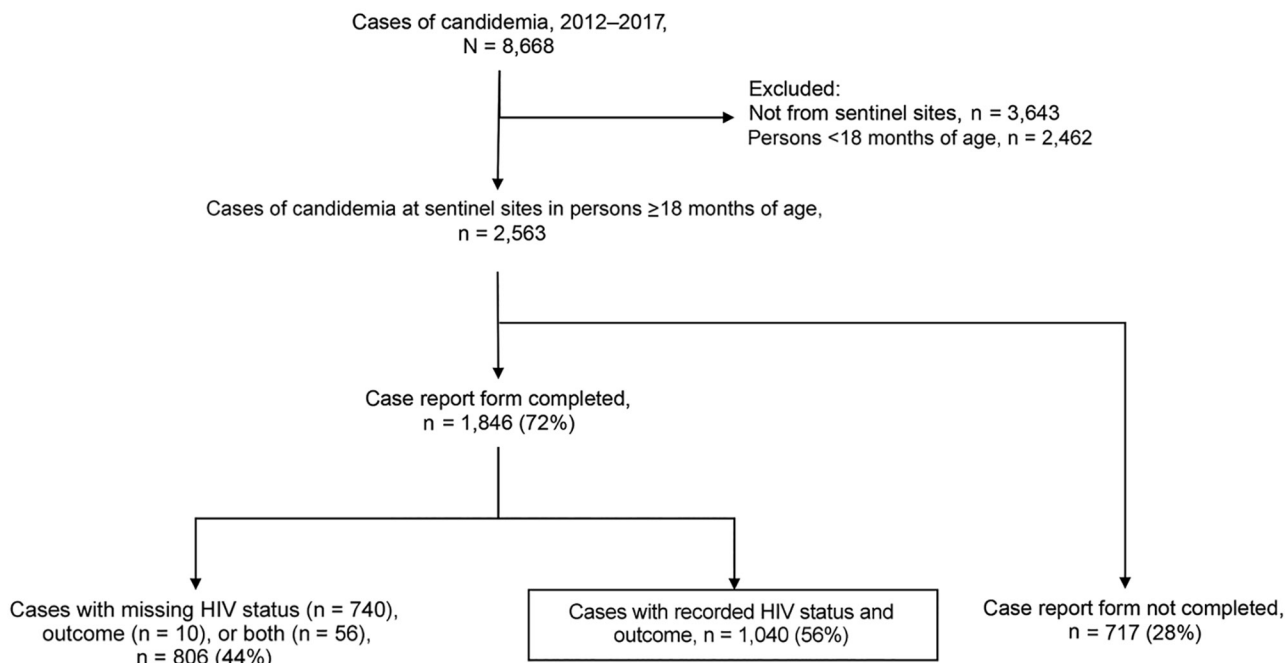
For GERMS-SA surveillance, annual ethics approvals were sought and obtained from several university ethics committees in South Africa. We also obtained approval from the London School of Hygiene and Tropical Medicine Research Ethics Committee.

### Results

After deduplication, 8,668 cases were detected by GERMS-SA surveillance during the 6-year period. We excluded 3,643 cases diagnosed at non-sentinel sites and 2,462 cases among infants and children  $<18$  months of age. Of 2,563 cases diagnosed at sentinel sites, a case report form had been completed for 1,846 (72%) (Figure 1). Of those, we retained 1,040 cases with both HIV status and outcome data (56%). We noted differences in age, sex, year of diagnosis, province in which the diagnosis was made, and *Candida* species among 717 sentinel-site cases with missing case report forms, 806 cases with completed case report forms but missing HIV status or outcome data, and the 1,040 cases included in the final analysis (Appendix Table 1).

### Description of 1,040 Participants Included in the Analysis

Of 1,040 participants, 542 (52%) were men and boys (Table 1, <https://wwwnc.cdc.gov/EID/article/27/6/21-0128-T1.htm>). The median age of 1,037 participants with recorded age was 37 years (interquartile range [IQR] 23–52 years). Of 1,035 participants with available date of specimen collection, 288 (28%) had a positive *Candida* blood culture within 72 hours of hospital admission. Overall, 50% (514/1,023) participants were managed in the ICU during their hospitalization (data on ICU admission were missing for 17 participants). At the time of diagnosis, most (545/1,011, 54%) had a central venous catheter (CVC) in situ, and 24% (245/1,004) were receiving total parenteral nutrition. Of 1,001 participants for whom data was available, 163 (16%) received previous antifungal treatment. A quick Pitt score was calculated for 652/1,040 participants: 319 (49%) had a 0 score, 184 (28%) had a 1 score, 126 (19%) had a 2 score, 20 (3%) had a 3 score, and 3 (1%) had a 4 score (Appendix). Thus, 149/652 (23%) had a quick Pitt score of  $\geq 2$ . Of 946 case-patients in which *Candida* species identification was performed at a diagnostic or reference laboratory, 521 (55%) participants were infected with a *Candida* species other than *C. albicans* and



**Figure 1.** Flowchart demonstrating selection of 1,040 cases of candidemia from a 6-year surveillance period for secondary data analysis, South Africa, 2012–2017.

the remainder with *C. albicans*; 33 (3%) case-patients had a mixed *Candida* infection. Of 1,010 cases, 700 (69%) received systemic antifungal treatment to treat candidemia (participants might have received  $\geq 1$  antifungal agent: fluconazole [ $n = 503$ ], amphotericin B [ $n = 265$ ], echinocandin [ $n = 91$ ], or voriconazole [ $n = 17$ ]). Of 764 cases with a known *Candida* species, available antifungal susceptibility data, and applicable Clinical and Laboratory Standards Institute breakpoints (18), 154 (20%) were infected with an antifungal-resistant species. Of these 764, antifungal treatment was recorded for 419, and 9% (38/419) had received inappropriate antifungal treatment. Of 488 cases with recorded information, 361 (74%) had their CVC removed after the candidemia diagnosis. In 4% of patients (45/1,040), evidence of complications of candidemia (deep organ involvement) was indicated in medical charts.

#### HIV Status and Outcome

Of the 1,040 case-patients, 426 (41%) were HIV-seropositive; we noted several differences in those patients compared with those who were HIV-seronegative (Table 1; Appendix). Among 404 HIV-seropositive persons with available data, 301 (75%) were antiretroviral treatment-experienced. Among 267 participants in whom CD4 count was recorded near the date of the candidemia diagnosis, the median CD4 count was 133 (IQR 42–309) cells/ $\mu\text{L}$ ; 166/267 (63%) had a CD4 count  $< 200$  cells/ $\mu\text{L}$ . An

additional 35 without a CD4 count had a recorded World Health Organization (WHO) clinical stage of HIV disease. Of these 35 case-patients, illness was WHO stage 3 or 4 in 33 case-patients. Of 141 whose records indicated a recently recorded viral load, 65 (46%) had a viral load of  $< 400$  RNA copies/mL. Of the 426 HIV-seropositive persons, 153 (36%) had clinical evidence of HIV-associated wasting. The overall case fatality ratio was 458/1,040 (44%). The case-fatality ratio among HIV-seronegative cases was 37% (230/614) versus 54% (228/426) for HIV-seropositive cases ( $p < 0.001$ ).

#### Risk Factors for 30-Day Mortality

The crude 30-day case fatality ratio among HIV-seropositive participants was 1.92 (95% CI 1.50–2.47) times higher than among HIV-seronegative participants ( $p < 0.001$ ) (Table 2, <https://wwwnc.cdc.gov/EID/article/27/6/21-0128-T2.htm>). After adjusting for sentinel hospital, age, sex, year of diagnosis, ICU admission, receipt of systemic antifungal treatment, and *Candida* species, the odds of 30-day mortality were still 1.89 (95% CI 1.38–2.60) times higher among HIV-seropositive participants than among HIV-seronegative participants (Table 3); evidence was strong against the null hypothesis ( $p < 0.001$ ). We noted relatively little confounding of the association between HIV status and 30-day mortality by any available explanatory variable. In the final



model, differences between hospitals accounted for 3% of the variability in deaths (intracluster correlation coefficient = 0.03;  $p = 0.003$ ). We found evidence of interaction of HIV status and ICU admission. The stratum-specific mortality OR was larger in the group not managed in an ICU (OR 2.27, 95% CI 1.47–3.52;  $p < 0.001$ ) than those who were admitted to the ICU (OR 1.56, 95% CI 1.00–2.43;  $p = 0.05$ ), although the 95% CIs overlapped (Table 4). In a dose-response analysis, the adjusted odds of 30-day mortality was 1.90 times higher among HIV-seropositive persons with a CD4 count  $\geq 200$  cells/ $\mu\text{L}$  (95% CI 1.13–3.20;  $p = 0.02$ ) and 2.18 times higher among persons with a CD4 count  $< 200$  cells/ $\mu\text{L}$  (95% CI 1.39–3.42;  $p = 0.001$ ) compared with 30-day mortality among HIV-seronegative persons (Appendix Table 4).

### Kaplan-Meier Survival Analysis

An outcome date was available for 1,023 participants. Overall, 44% (452/1,023) died within 30 days. The Kaplan-Meier survival curves diverged for HIV-seropositive and HIV-seronegative persons within 3 days of candidemia diagnosis and then remained roughly parallel until day 30 (Figure 2). Evidence was strong against the hypothesis that survival experience did not differ by HIV status ( $p < 0.001$ ).

### Association of HIV Status and ICU Admission

Among 1,023 participants, a lower proportion (175/422, 41%) of HIV-seropositive persons than HIV-seronegative persons (339/601, 56%) were admitted to the ICU (crude OR 0.55, 95% CI 0.42–0.71;  $p < 0.001$ ). After adjustment for sentinel site, age, sex, and quick Pitt score category ( $n = 583$ ) (Appendix Table 5), HIV-seropositive participants were 60% less likely to be admitted to the ICU than HIV-seronegative participants (OR 0.40, 95% CI 0.25–0.64;  $p < 0.001$ ). Among HIV-seropositive participants, a similar proportion with and without advanced HIV disease were admitted to the ICU (72/166 [43%] vs. 39/99 [39%];  $p = 0.53$ ). A similar proportion of HIV-seropositive participants receiving and not receiving antiretroviral treatment were admitted to ICU (116/299 [39%] vs. 50/101 [50%];  $p = 0.06$ ).

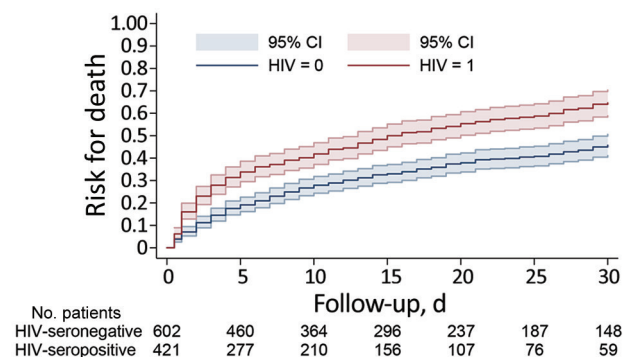
### Discussion

In this surveillance study of hospitalized persons with candidemia in South Africa, the prevalence of HIV infection was 41% (95% CI 38%–44%). The 30-day mortality rate was almost twice as high among HIV-seropositive persons as among HIV-seronegative persons (OR 1.89, 95% CI 1.38–2.60;  $p < 0.001$ ), after adjusting for relevant confounders. The effect of HIV infection on death rates was estimated to be stronger among

**Table 3.** Random-effects multivariable logistic regression analysis of the effect of HIV on in-hospital death by sentinel site, simultaneously adjusted for potential confounders, among 907 persons with candidemia, South Africa, 2012–2017\*

Variable	Summary aOR for death (95% CI)	Wald p value
HIV status		
Seronegative	Referent	
Seropositive	1.89 (1.38–2.60)	<0.001
Age group, y		
<18	Referent	
18–44	2.55 (1.66–3.93)	<0.001
45–64	3.48 (2.21–5.49)	<0.001
>65	6.47 (3.61–11.61)	<0.001
Sex		
F	Referent	
M	1.27 (0.95–1.70)	0.11
Year		
2012	Referent	
2013	1.26 (0.72–2.19)	0.42
2014	1.34 (0.67–2.68)	0.40
2015	1.17 (0.58–2.33)	0.66
2016	1.08 (0.63–1.86)	0.77
2017	1.53 (0.90–2.61)	0.12
ICU admission		
No	Referent	
Yes	1.70 (1.23–2.36)	0.001
Receipt of systemic antifungal treatment		
No	Referent	
Yes	0.35 (0.25–0.48)	<0.001
<i>Candida</i> species		
<i>C. albicans</i>	Referent	
Other <i>Candida</i> spp.	0.66 (0.49–0.89)	0.006

\*aOR, adjusted odds ratio; ICU, intensive care unit. Intra-cluster correlation coefficient = 0.03; likelihood ratio test for  $\rho = 0$ ; p value = 0.003.



**Figure 2.** Kaplan-Meier analysis for 1,023 participants with candidemia during a 30-day period after the diagnosis of culture-confirmed candidemia by HIV infection status (outcome date missing for 17 participants), South Africa, 2012–2017. HIV = 0: HIV-seronegative; HIV = 1: HIV-seropositive; p value for log-rank test <0.001.

those not managed in an ICU than those who were, though the 95% CIs overlapped. HIV-seropositive persons also had a substantially lower risk for ICU treatment during their admission than those who were HIV-seronegative.

The overall crude mortality rate associated with candidemia of 44% (95% CI 41%–47%) reported in this study is higher than that reported in resource-rich settings (19), possibly owing to differences in our hospitalized cohort. The overall median age was lower, a large proportion were critically ill, and amphotericin B deoxycholate and azoles were the mainstay of treatment, whereas few patients received echinocandins. In our large study, we found a crude mortality rate among HIV-seropositive patients of 54%, which is comparable to the 60% mortality rate reported in 2 case series (6,7). Our main results are consistent with a United States cohort study that found that HIV infection was associated with a 2-fold increased adjusted hazard of 30-day mortality (9). We believe that this association between HIV and death among persons with candidemia is biologically plausible. First, the mechanism for an increased risk for death among HIV-seropositive persons may operate at the

individual level. Despite a large proportion having received previous antiretroviral treatment, the median CD4 count among hospitalized HIV-seropositive participants with candidemia in this study was 133 cells/ $\mu$ L, and almost two thirds had advanced HIV disease (defined by the WHO as a CD4 count of <200 cells/ $\mu$ L) (20). This finding is consistent with reports of virologic failure and treatment interruption among an increasing proportion of HIV-seropositive patients at acute-care hospitals in South Africa (21). Many persons with advanced HIV disease have neutropenia or neutrophil defects (10,11). This innate immune defect may be a consequence of abnormal progenitor stem cell growth, a deficiency of granulocyte colony-stimulating factor, bone marrow infiltration by opportunistic infectious agents or malignant cells, treatment with particular medicines, or autoimmune phenomena (10). The alteration in the innate immune response may then reduce the clearance of *Candida* from the bloodstream, despite appropriate antifungal treatment. People with advanced HIV disease might also have been admitted primarily for management of disseminated tuberculosis, cryptococcal disease, or *Pneumocystis pneumonia*, which are associated with high death rates (20). In addition, more than one third of HIV-seropositive participants in this study were recorded to have evidence of HIV-associated wasting. Patients with a poorer nutritional state or loss of lean body mass have worse outcomes (22).

Second, an increased risk for death may be a consequence of differential treatment practices at the sentinel hospitals for HIV-seronegative and HIV-seropositive persons. We found that HIV-seropositive persons were 60% less likely to have received intensive care during their hospitalization. Several studies in Italy have documented the large proportion of patients who are managed for candidemia in general medical wards (23–25). In addition, the adjusted effect of HIV infection on 30-day mortality rates was stronger among participants who were not managed in an ICU during their hospital stay. This finding suggests that intensive care and monitoring of patients

**Table 4.** Interaction between HIV and intensive care unit admission on in-hospital death among 907 persons with candidemia, adjusted for potential confounders, South Africa, 2012–2017\*

Variable	Stratum-specific aOR for death (95% CI)	Wald test p value†
Admitted to ICU		
HIV-seronegative	Referent	
HIV-seropositive	1.56 (1.00–2.43)	0.05
Not admitted to ICU		
HIV-seronegative	Referent	
HIV-seropositive	2.27 (1.47–3.52)	<0.001

\*aOR, adjusted odds ratio; ICU, intensive care unit.

†Overall likelihood ratio test for interaction p value = 0.22. Case-fatality ratio for those admitted to an ICU: HIV-seropositive (94/152; 62%), HIV-seronegative (157/301; 52%) versus those not admitted to an ICU: HIV-seropositive (117/224; 52%), HIV-seronegative (76/230; 33%).

with candidemia, including those who are HIV-seropositive, might reduce mortality rates. However, in a resource-limited setting, the number of ICU beds is restricted. The criteria for admission to a public-sector ICU in South Africa includes an assessment of the severity of the acute or underlying illness and whether organ dysfunction can realistically be reversed. These criteria apply equally to those with and without HIV infection, according to a survey of critical care physicians in South Africa, although no data exist on the proportion of HIV-seropositive persons who were eligible for ICU admission but were not referred or were turned down (26,27). Among HIV-seropositive participants in our study, similar proportions of persons with advanced HIV disease who were receiving antiretroviral treatment were or were not admitted to ICU, suggesting that these factors were not the sole criteria for admission.

We confirmed several well-described risk factors for death among patients with candidemia, including inappropriate or no antifungal treatment, ICU admission, increased age, and a quick Pitt score of  $\geq 2$  (28). Removal of a CVC following diagnosis of candidemia was protective against death. A limitation of this study is that it was a secondary data analysis and was not specifically designed or powered to answer whether HIV infection was associated with death among patients with candidemia. However, the study was conducted in a high HIV prevalence setting, our sample size was large, and we found strong and consistent evidence against the null hypothesis after adjustment for confounding. Selection bias was a limitation because we excluded 60% of cases diagnosed at sentinel hospitals for whom data for the main exposure and outcome variables were missing. We also found differences among those who were included and excluded from the analysis. For instance, we included a larger proportion of cases among adults 18–44 years of age, cases caused by *C. albicans*, and cases from outside Gauteng Province in the analysis (Appendix). Data were also missing for confounder variables, and we excluded several potentially critical confounders from the main multivariable analysis. However, including these variables in a smaller dataset for multivariable analysis did not change the point estimate for the main exposure effect, although the 95% CI was wider (Appendix Table 3). In  $\approx 20\%$  of cases, HIV status was self-reported by participant or next-of-kin interview if a clear record of HIV status was not in the chart. If HIV-seropositive persons underreported their actual infection status, it might have weakened the association with death demonstrated in this study. Because we were unable

to adjust for unmeasured factors, such as the presence or severity of diagnosed or undiagnosed underlying conditions, residual confounding is also possible. We conducted this study in an upper middle-income country, and participants were recruited at urban sentinel hospitals with ICU facilities; therefore, the results might not apply to all hospital populations. Cause of death was not recorded, and we were thus unable to estimate the number of deaths directly attributable to candidemia among either HIV-seropositive or HIV-seronegative participants. We excluded children  $< 18$  months of age from this analysis and cannot comment on whether HIV exposure or infection is associated with death in this population.

A key strength of this study was that it was nested within a large active surveillance system; laboratory audits were conducted to ensure that all culture-confirmed cases were captured. The main outcome measure was in-hospital death, a clear endpoint that was unlikely to have been misclassified. Given that most persons with HIV infection live in sub-Saharan Africa and the risk for healthcare-associated infections, including those caused by antimicrobial-resistant fungi, is becoming increasingly critical in this region (1,29–31), our findings might have broader implications than similar studies and are an essential addition to the literature.

In conclusion, we found that the overall crude mortality rate associated with candidemia was high, and HIV-seropositive persons were at  $\approx 2$ -fold increased adjusted risk for all-cause in-hospital death, compared with their HIV-seronegative counterparts. This effect on mortality rates was weakened among those admitted to the ICU, though HIV-seropositive persons were substantially less likely to have received intensive care. We recommend a high index of suspicion for candidemia among admitted HIV-seropositive persons, regardless of the presence of classical risk factors. We further recommend that HIV-seropositive persons with suspected candidemia rapidly begin appropriate early antifungal treatment, that they be investigated to identify an infection source and control measures instituted, and that they should be considered for intensive care and monitoring to reduce deaths. Where feasible, consultation with an infectious disease specialist would enable this level of care.

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# HIV Infection as Risk Factor for Death among Hospitalized Persons with Candidemia, South Africa, 2012–2017

## Appendix

### Supplementary Methods

#### Sentinel Hospital and Diagnostic Laboratory Practices

Attending clinicians initiated empiric antifungal treatment when an episode of candidemia was suspected. Amphotericin B deoxycholate and fluconazole was widely available, but echinocandin treatment was limited to private-sector hospitals and academic public-sector hospitals. Blood culture specimen collection practices varied widely among provinces and between the private and public sector (1). Diagnostic laboratories serving the sentinel hospitals used automated blood culturing systems such as Bactec (BD, <https://www.bd.com>) and processed specimens by using standard operating procedures.

#### Confounding and Interaction

We regrouped potential confounder variables into clinically meaningful categories. Intensive care unit (ICU) admission was recorded as a binary variable as a response to the question: Has the participant ever been admitted for intensive care during this hospital admission? The Pitt bacteremia score, a marker of disease severity, is as accurate as the APACHE II score for predicting death among critically ill persons with sepsis and has also been shown to be associated with death among persons with candidemia (2,3). We calculated a quick Pitt score, an abbreviated version of the Pitt bacteremia score, as the sum of individual scores for body temperature of  $<35^{\circ}\text{C}$  (1 point), systolic blood pressure of  $<90$  mm Hg (1 point), cardiac arrest (1 point), mechanical ventilation (1 point), and altered mental status (1 point) on the day of diagnosis of candidemia. A quick Pitt score of  $\geq 2$  was strongly correlated with a Pitt bacteremia score of  $\geq 4$  and predicted death in patients with carbapenem-resistant Enterobacterales infections (4). Antifungal resistance was defined on the basis of Clinical and Laboratory Standards Institute

M60 *Candida* species-specific breakpoints for MICs (MIC); this was restricted to species or antifungal agents for which breakpoints have been published (5). Inappropriate antifungal treatment was defined as treatment around the time of diagnosis with an antifungal agent to which the *Candida* species was resistant. We defined a mixed episode of candidemia as >1 *Candida* spp. either cultured from a single blood culture specimen or from multiple specimens over the 30-day period. We defined community-onset infection as a positive blood culture within 72 hours of hospital admission. We considered age and sex to be important a priori confounders. We screened potential confounders by cross-tabulating these variables with the main exposure and looked for associations in our dataset. None of the potential confounders were considered to be on the causal pathway for the main study question. We decided that the following potential confounding variables had collinear relationships with the main exposure: ICU admission, central venous catheter in situ, and total parenteral nutrition. We chose to use ICU admission in our models.

### **Classical Analyses**

We looked for evidence that the effect estimate for the association between HIV status and 30-day mortality was confounded or modified by each explanatory variable. We compared the summary weighted odds ratio (OR) to the crude OR and looked for a  $\approx 10\%$  change in main exposure effect estimate as evidence of confounding. We also visually compared the stratum-specific ORs across each level of the potential effect-modifying variable and performed a test of homogeneity of ORs.

### **Model Building**

We omitted potential confounders with a large amount of missing data. We checked the number of events and then applied a rule of ten (events per variable) to ensure that the models included a reasonable number of parameters. We forced the prespecified confounder variables (i.e., age, sex) into a baseline model and then added other potential confounders, one at a time using a forward approach, starting with the variable with the strongest association with death on univariable analysis. We retained a potential confounder in the model if this changed the main effect estimate by 10% and then added the other variables in turn. We checked the reliability of parameter estimates by using the `quadchk` command in Stata (<https://www.stata.com>) because the number of participants within many of the 29 clusters was large (>20). We compared the

final logistic regression models with and without an interaction term between HIV status and ICU admission.

## **Supplementary Results**

### **Description of 1,040 Cases Included in Analysis**

The number of sentinel sites and thus the number of cases varied by year of surveillance: 2012 (9 sites in Gauteng/Western Cape, 139 cases), 2013 (10 sites in Gauteng/Western Cape, 185 cases), 2014 (17 sites in other 7 provinces, 100 cases), 2015 (20 sites in other 7 provinces, 91 cases), 2016 (25 sites in all provinces, 273 cases), 2017 (27 sites in all provinces, 252 cases). All sites were public-sector hospitals except 3 private hospital sites that participated in 2016 and 2017. We conducted a complete records analysis. Among 1,040 cases included in this analysis, 730 (70%) case report forms were completed by interview plus medical chart review versus 310 (30%) by retrospective medical chart review alone. In general, the completeness of case report forms was better for participants who were interviewed and had their medical charts prospectively reviewed. Among the 806 cases that were excluded because of missing HIV status or outcome data, 374 (46%) had case report forms completed by interview or medical chart review versus 432 (54%) by medical chart review alone ( $p < 0.001$ ). The median time of survival among 307 participants who did not receive systemic antifungal treatment was 3 days (interquartile range [IQR] 1–10 days) from the positive blood culture date versus 16 days (IQR 8–32 days) among 686 who received treatment.

### **Comparison of HIV-Seropositive and HIV-Seronegative Persons**

Compared with 614 HIV-seronegative participants with candidemia, a larger proportion of their HIV-seropositive counterparts were 18–44 years of age (237/425 [56%] vs. 190/612 [31%];  $p < 0.001$ ), female (226/426 [53%] vs. 272/614 [44%];  $p = 0.005$ ), received a diagnosis later in the surveillance period (2015–2017) (263/426 [62%] vs. 353/614 [57%];  $p < 0.001$ ), not admitted to an ICU (247/422 [59%] vs. 262/601 [44%];  $p < 0.001$ ), not receiving total parenteral nutrition (334/412 [81%] vs. 425/592 [72%];  $p < 0.001$ ), not receiving fluids or medicines through a central venous catheter (CVC) (223/414 [54%] vs. 243/597 [41%];  $p < 0.001$ ), infected with *C. albicans* (204/389 [52%] vs. 221/557 [40%];  $p < 0.001$ ), not infected with an antifungal-resistant *Candida* spp. (265/305 [87%] vs. 345/459 [75%];  $p < 0.001$ ) and not receiving systemic



antifungal treatment around the time of candidemia diagnosis (157/415 [38%] vs. 153/595 [26%];  $p < 0.001$ ) (Table 1 in the main text). A similar proportion of HIV-seropositive and HIV-seronegative persons had recorded evidence of complications of candidemia (deep organ involvement) in their medical charts (17/426 [4%] vs. 28/614 [5%];  $p = 0.66$ ).

### **Unadjusted Risk Factors for 30-Day Mortality**

The case fatality ratio was incrementally higher in each of the 3 older age groups compared with the baseline category (i.e., 18 months–17 years) ( $p < 0.001$ ) (Table 2 in the main text). ICU admission was associated with a 43% increased crude risk for death (95% CI 1.11–1.83;  $p = 0.005$ ). For 652 participants with a quick Pitt score, a score of  $\geq 2$  was associated with a 2.49 increased risk for 30-day mortality (95% CI 1.71–3.61;  $p < 0.001$ ). Compared with *C. albicans* infection, infection with a species other than *C. albicans* was associated with a 41% reduced crude odds of death (95% CI 0.46–0.77;  $p < 0.001$ ). Receipt of systemic antifungal treatment around the time of candidemia diagnosis was associated with a 63% reduced odds of 30-day mortality (95% CI 0.28–0.49;  $p < 0.001$ ). Among 488 participants with available data, removal of an indwelling CVC was protective against death (OR 0.51, 95% CI 0.34–0.76;  $p < 0.001$ ).

### **Classical Stratified Analysis of the Relationship between HIV Status and 30-Day Mortality**

Upon classical stratified analysis, the summary odds of death at 30 days remained approximately 2-fold higher among HIV-seropositive participants versus HIV-seronegative participants with candidemia when adjusted for each potential confounder in turn. We found consistently strong evidence against the null hypothesis of an OR = 1 ( $p < 0.001$  in all cases, except when adjusting for inappropriate antifungal treatment) (Appendix Table 2). ICU admission was a negative confounder of the association between HIV and 30-day mortality; the point estimate for the summary mortality OR shifted by  $>10\%$  from 1.89 (95% CI 1.38–2.60) to 2.09 (95% CI 1.60–2.71) after adjusting for this variable. A quick Pitt score of  $\geq 2$  was also a negative confounder; the point estimate changed to 2.28 (95% CI 1.63–3.18) after adjustment. Conversely, the summary OR point estimate shifted  $\approx 10\%$  lower to 1.72 (95% CI 1.13–2.61) when we adjusted for inappropriate antifungal treatment. However, as already noted, we had a large amount of missing data for both the latter variables.

Using a low-power test for interaction, we did not find strong evidence of an interaction between HIV status and any other variable when comparing 30-day mortality rates among HIV-seropositive persons with those of HIV-seronegative persons. Conversely, upon visual inspection of the stratum-specific rate ratios in Appendix Table 2, we identified the following as possible effect modifiers (different stratum-specific OR point estimates but overlapping 95% CI): age, sex, year of diagnosis, ICU admission, inappropriate antifungal treatment, and removal of the CVC. However, we focused only on ICU admission as an effect modifier because we had specified this a priori.

### **Random-Effects Multivariable Logistic Regression Analysis**

We conducted a 2-level random-effects multivariable logistic regression analysis. We excluded 133 cases with missing data for any of the confounders; thus, the final model included 907 participants. We excluded quick Pitt score and inappropriate antifungal treatment from the final analysis because there were large amounts of missing data, even though these were potentially important confounders. However, when these variables were retained in a model with fewer observations ( $n = 263$ ), the point estimate for the effect of HIV infection on mortality rates was very similar to that described in the final model (Appendix Table 3).

### **Dose-Response Effect of HIV Infection**

We considered HIV status as an ordinal variable: HIV-seronegative, HIV-seropositive without advanced immunosuppression (CD4 count  $\geq 200$  cells/ $\mu$ L), and HIV-seropositive with advanced immunosuppression (CD4 count  $< 200$  cells/ $\mu$ L). We then adjusted for sentinel hospital, age, sex, year of diagnosis, ICU admission, receipt of systemic antifungal treatment, and *Candida* species in a 2-level random effects model ( $n = 767$ ) (Appendix Table 4). Compared with mortality among HIV-seronegative persons, the adjusted odds of 30-day mortality was 1.90 times higher among HIV-seropositive persons without advanced immunosuppression (95% CI 1.13–3.20;  $p = 0.02$ ) and 2.18 times higher among persons with advanced HIV disease (95% CI 1.39–3.42;  $p = 0.001$ ). After adjustment for sentinel site, age, sex, and quick Pitt score category ( $n = 583$ ) (Appendix Table 5), HIV-seropositive persons had a 60% reduced risk for ICU admission compared with HIV-seronegative participants (OR 0.40, 95% CI 0.25–0.64;  $p < 0.001$ ).

## Supplementary Discussion

In 2 small studies of HIV-seropositive participants with candidemia, infection with a species other than *C. albicans* was independently associated with death (6,7). On the basis of these previous reports, we initially hypothesized that HIV-seropositive persons would be more likely to be infected with a species other than *C. albicans*. Since these species are more likely to be antifungal-resistant, we then speculated that death would be more likely in this group because of inappropriate antifungal treatment. However, we found that HIV-seropositive participants had a 34% lower odds of being infected with *Candida* species other than *C. albicans*. This is also consistent with our finding that almost a third of HIV-seropositive persons may have acquired candidemia as a community-onset infection, though a similarly large proportion of HIV-seronegative persons also had a diagnosis within 72 hours of admission. We did not collect information on all healthcare contacts in the preceding 12 months so could not exclude that these infections were healthcare-associated. Community-onset infections in HIV-seropositive persons have been documented in a single-center study in South Africa (8). Despite its susceptibility to most antifungal agents, *C. albicans*, a common component of the gastrointestinal microbiota, has a well-described array of virulence factors that may increase severity of illness and risk for death (9). In a study in Italy, persons with candidemia caused by >1 *Candida* spp. versus monomicrobial infection were more likely to be HIV-seropositive (2/15 vs. 14/737). In turn, mixed candidemia was independently associated with increased deaths; the authors hypothesized that this effect was mediated by a larger fungal bloodstream burden in mixed infections (10). In our study, only 3% of patients had a mixed infection, and proportions were similar in HIV-seropositive groups and HIV-seronegative groups.

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**Appendix Table 1.** Characteristics of 2,563 patients with candidemia at sentinel sites who were included or excluded from analysis of HIV infection as risk factor for death, South Africa, 2012–2017

Variable	No. patients	Excluded from analysis		Included in analysis	p value*
		Case report form not completed (n = 717)	Case report form completed but missing HIV status or outcome data (n = 806)	Case report form completed including HIV status and outcome data (n = 1040)	
Age group, y					
<18	478	58 (12)	194 (41)	226 (47)	<0.001
18–44	742	126 (17)	189 (25)	427 (58)	
45–64	652	145 (22)	224 (34)	283 (43)	
≥65	389	113 (29)	175 (45)	101 (26)	
Missing	302	275 (91)	24 (8)	3 (1)	
Sex					
F	1,003	167 (16)	338 (34)	498 (50)	0.04
M	1,199	191 (16)	466 (39)	542 (45)	
Missing	361	359 (99)	2 (1)	0 (0)	
Year					
2012	330	142 (43)	49 (15)	139 (42)	<0.001
2013	321	61 (19)	75 (23)	185 (58)	
2014	161	17 (11)	44 (27)	100 (62)	
2015	162	14 (9)	57 (35)	91 (56)	
2016	754	249 (33)	232 (31)	273 (36)	
2017	835	234 (28)	349 (42)	252 (30)	
Missing	0	0 (0)	0 (0)	0 (0)	
Province					
Other province	845	97 (11)	253 (30)	495 (59)	<0.001
Gauteng	1,715	617 (36)	553 (32)	545 (31)	
Missing	3	3 (100)	0 (0)	0 (0)	
<i>Candida</i> species					
<i>Candida albicans</i>	790	109 (14)	256 (32)	425 (54)	<0.001
Other <i>Candida</i> species	1,504	517 (34)	466 (31)	521 (35)	
Missing	269	91 (34)	84 (31)	94 (35)	

\*P value by Pearson's  $\chi^2$  test (excluding missing category) to compare 3 groups.

**Appendix Table 2.** Effect of HIV infection on 30-day mortality rate among 1,040 persons with candidemia, adjusted in turn for each potential confounder, South Africa, 2012–2017\*

Variable	No. patients	Stratum-specific OR (95% CI)	Mantel-Haenszel summary OR (95% CI)	Score test p value	p value for test of interaction
Age group, y					
<18	226	1.11 (0.54–2.25)	2.03 (1.54–2.68)	<0.001	0.21
18–44	427	2.61 (1.73–3.92)			
45–64	283	1.94 (1.18–3.19)			
≥65	101	1.56 (0.44–5.50)			
Sex					
F	498	1.56 (1.09–2.23)	1.94 (1.50–2.50)	<0.001	0.09
M	542	2.42 (1.68–3.48)			
Year					
2012	139	1.31 (0.63–2.75)	1.85 (1.43–2.39)	<0.001	0.21
2013	185	1.59 (0.86–2.93)			
2014	100	2.44 (1.06–5.59)			
2015	91	0.80 (0.35–1.86)			
2016	273	2.29 (1.37–3.84)			
2017	252	2.41 (1.43–4.05)			
ICU admission					
No	509	2.46 (1.69–3.58)	2.09 (1.60–2.71)	<0.001	0.21
Yes	514	1.76 (1.21–2.56)			
CVC in situ					
No	466	1.95 (1.33–2.84)	2.05 (1.57–2.67)	<0.001	0.71
Yes	545	2.15 (1.49–3.10)			
Total parenteral nutrition					
No	759	1.90 (1.42–2.55)	1.98 (1.53–2.58)	<0.001	0.55
Yes	245	2.31 (1.32–4.04)			
Quick Pitt score of ≥2†					
No	503	2.28 (1.57–3.33)	2.28 (1.63–3.18)	<0.001	0.98
Yes	149	2.26 (1.11–4.62)			
<i>Candida</i> species					
<i>Candida albicans</i>	425	1.98 (1.34–2.93)	1.74 (1.33–2.28)	<0.001	0.37
Other <i>Candida</i> species	521	1.55 (1.07–2.24)			
<i>Candida</i> species resistant to fluconazole, voriconazole or an echinocandin‡					
No	610	1.97 (1.42–2.73)	1.93 (1.43–2.61)	<0.001	0.78
Yes	154	1.76 (0.84–3.66)			
Receipt of systemic antifungal treatment					
No	310	1.95 (1.22–3.12)	1.78 (1.37–2.32)	<0.001	0.64
Yes	700	1.71 (1.24–2.35)			
Inappropriate antifungal treatment for candidemia§					
No	381	1.78 (1.15–2.75)	1.72 (1.13–2.61)	0.01	0.58
Yes	38	1.13 (0.25–5.23)			
Removal of CVC					
No	127	2.57 (1.20–5.53)	1.99 (1.35–2.94)	<0.001	0.44
Yes	361	1.81 (1.15–2.85)			

\*CVC, central venous catheter; ICU, intensive care unit; OR, odds ratio.

†Quick Pitt score was calculated as the sum of individual scores for temperature <35°C (1), systolic blood pressure <90 mm Hg (1), cardiac arrest (1), mechanical ventilation (1), and altered mental status (1) at time of diagnosis of candidemia.

‡Resistance was defined on the basis of Clinical and Laboratory Standards Institute M60 *Candida* species-specific breakpoints.

§Inappropriate treatment was defined as treatment with an antifungal agent to which the *Candida* species was resistant.

**Appendix Table 3.** Random-effects multivariable logistic regression analysis of the effect of HIV on 30-day mortality rates by potential confounder among 263 persons with candidemia, South Africa, 2012–2017\*

Variable	Summary aOR for death (95% CI)	Wald p value
HIV status		
Seronegative	1	
Seropositive	1.79 (0.96–3.35)	<0.07
Age group, y		
<18	1	
18–44	1.62 (0.70–3.75)	0.26
45–64	3.11 (1.30–7.45)	0.01
≥65	5.50 (1.96–15.48)	0.001
Sex		
F	1	
M	1.40 (0.80–2.43)	0.24
Year		
2012	1	
2013	1.35 (0.55–3.33)	0.51
2014	1.64 (0.57–4.74)	0.36
2015	0.82 (0.23–2.90)	0.76
2016	0.60 (0.23–1.60)	0.31
2017	1.83 (0.77–4.37)	0.17
ICU admission		
No	1	
Yes	1.10 (0.55–2.17)	0.80
Receipt of systemic antifungal treatment		
No	1	
Yes	Omitted from model	
<i>Candida</i> species		
<i>Candida albicans</i>	1	
Other <i>Candida</i> species	0.96 (0.53–1.73)	0.89
Quick Pitt score of ≥2†		
No	1	
Yes	1.64 (0.81–3.32)	0.17
Inappropriate antifungal treatment for candidemia‡		
No	1	
Yes	0.87 (0.31–2.40)	0.78

\*Data sparsity in this model may affect estimates. Intraclass correlation coefficient < 0.001; likelihood ratio test for  $\rho = 0$ ; p value = 0.50. aOR, adjusted odds ratio; ICU, intensive care unit.

†Quick Pitt score was calculated as the sum of individual scores for temperature <35°C (1), systolic blood pressure <90 mm Hg (1), cardiac arrest (1), mechanical ventilation (1), and altered mental status (1) at time of diagnosis of candidemia.

‡Resistance was defined on the basis of Clinical and Laboratory Standards Institute M60 *Candida* species-specific breakpoints. Inappropriate treatment was defined as treatment with an antifungal agent to which the *Candida* species was resistant.

**Appendix Table 4.** Random-effects multivariable logistic regression analysis of the effect of HIV as an ordinal variable on 30-day mortality rates by potential confounder among 767 persons with candidemia, South Africa, 2012–2017\*

Variable	Summary aOR for death (95% CI)	Wald p value
HIV status		
Seronegative	1	
Seropositive with CD4 count $\geq 200$ cells/ $\mu$ L	1.90 (1.13–3.20)	0.02
Seropositive with CD4 count $< 200$ cells/ $\mu$ L	2.18 (1.39–3.42)	0.001
Age group, y		
<18	1	
18–44	2.25 (1.38–3.67)	0.01
45–64	3.20 (1.93–5.31)	<0.001
$\geq 65$	5.65 (3.01–10.57)	<0.001
Sex		
F	1	
M	1.31 (0.95–1.82)	0.10
Year		
2012	1	
2013	0.97 (0.53–1.78)	0.92
2014	1.14 (0.53–2.43)	0.74
2015	1.05 (0.49–2.24)	0.89
2016	0.90 (0.50–1.62)	0.73
2017	1.48 (0.83–2.64)	0.19
ICU admission		
No	1	
Yes	1.92 (1.34–2.74)	<0.001
Receipt of systemic antifungal treatment		
No	1	
Yes	0.31 (0.21–0.46)	<0.001
Candida species		
<i>Candida albicans</i>	1	
Other <i>Candida</i> species	0.65 (0.47–0.90)	0.01

\*Intraclass correlation coefficient = 0.04; likelihood ratio test for  $\rho = 0$ ; p value = 0.003. aOR, adjusted odds ratio; ICU, intensive care unit.

**Appendix Table 5.** Random-effects multivariable logistic regression analysis of the effect of HIV infection on intensive care unit admission by sentinel site, age, sex, and quick Pitt score category among 583 persons with candidemia, South Africa, 2012–2017\*

Variable	Summary aOR for ICU admission (95% CI)	Wald p value
HIV status		
Seronegative	1	
Seropositive	0.40 (0.25–0.64)	<0.001
Age group, y		
<18	1	
18–44	3.22 (1.72–6.04)	<0.001
45–64	2.51 (1.28–4.90)	0.007
$\geq 65$	3.44 (1.37–8.67)	0.009
Sex		
F	1	
M	0.84 (0.55–1.31)	0.46
Quick Pitt score of $\geq 2$ †		
No	1	
Yes	23.81 (11.57–49.02)	<0.001

\*aOR, adjusted odds ratio; ICU, intensive care unit. Intraclass correlation coefficient = 0.39; likelihood ratio test for  $\rho = 0$ ; p value < 0.001.

†Quick Pitt score was calculated as the sum of individual scores for temperature  $< 35^\circ\text{C}$  (1), systolic blood pressure  $< 90$  mm Hg (1), cardiac arrest (1), mechanical ventilation (1), and altered mental status (1) at time of diagnosis of candidemia.