Improving one-year mortality following Intensive Care Unit admission in adults with HIV: a 20-year observational study

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ABSTRACT

Background: Despite widespread use of combination antiretroviral therapy, people with HIV (PWH) continue to have an increased risk of admission to and mortality in the intensive care unit (ICU). Mortality risk after hospital discharge is not well described. Using retrospective data on adult PWH ($\geq$18 years) admitted to ICU from 2000-2019 in an HIV-referral centre, we describe trends in 1-year mortality after ICU admission.

Methods: One-year mortality was calculated from index ICU admission to date of death; with follow-up right-censored at day 365 for people remaining alive at 1 year, or day 7 after ICU discharge if lost-to-follow-up after hospital discharge. Cox regression was used to describe the association with calendar year before and after adjustment for patient characteristics (age, sex, Acute Physiology and Chronic Health Evaluation II [APACHE II] score, CD4+ T-cell count, and recent HIV diagnosis) at ICU admission. Analyses were additionally restricted to those discharged alive from ICU using a left-truncated design, with further adjustment for respiratory failure at ICU admission in these analyses.

Results: 221 PWH were admitted to ICU (72% male, median [interquartile range (IQR)] age 45 [38-53] years) of whom 108 died within 1-year (cumulative 1-year survival: 50%). Overall, the hazard of 1-year mortality was decreased by 10% per year (crude hazard ratio (HR): 0.90 (95% confidence interval: 0.87-0.93)); the association was reduced to 7% per year (adjusted HR: 0.93 (0.89-0.98)) after adjustment. Conclusions were similar among the subset of 136 patients discharged alive (unadjusted: 0.91 (0.84-0.98); adjusted 0.92 (0.84, 1.02)).

Conclusions: Between 2000 and 2019, 1-year mortality after ICU admission declined at this ICU. Our findings highlight the need for multi-centre studies; and the importance of continued engagement in care after hospital discharge among PWH.

Key words: outcome, mortality, survival, intensive care unit, intensive care, APACHE II, HIV, AIDS, antiretroviral therapy, people with HIV, CD4+ T-cell count, viral load

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INTRODUCTION

The pattern of critical illness in people with HIV (PWH) has evolved since the introduction of the first antiretroviral agent in the 1990s, with fewer AIDS-defining illnesses and a greater proportion of hospital admissions due to complications of treatment and decompensation of comorbid diseases.[1–5] Among PWH admitted to the intensive care unit (ICU), short-term outcomes (survival to ICU and hospital discharge) following ICU admission have improved since the 1980s, partly due to improvements in ICU care and partly as a result of the changing pattern of causes of admission; outcomes are now similar to those seen among those admitted to ICU more generally.[1,3–9]

Evidence regarding longer-term outcomes is less clear. Survival rates of 25-80% at 6 months[8–13] and 25-66% at 1 year[9,10,12,14–18] among PWH have been reported. These studies inconsistently describe factors present at ICU admission that are associated with longer-term outcomes including older age, low CD4+ T-cell count, previous AIDS diagnosis, receipt of ART, low serum albumin, need for mechanical ventilation, and illness severity scores such as the Veterans Aging Cohort Study (VACS) Index, the Simplified Acute Physiology Score (SAPS), or the Acute Physiology and Chronic Health Evaluation II score (APACHE II).[8–10,12,14,16,17,19]

In this study we aimed to describe 1-year mortality in adult people with HIV admitted to a single university-affiliated hospital ICU to identify trends and to ascertain which demographic and clinical factors recorded on ICU admission were associated with 1-year mortality.

METHODS

Patient Population and Data Sources

We conducted a retrospective observational study using data on all adult PWH (at least 18 years of age) admitted to the Royal Free Hospital (RFH) ICU between 1 January 2000 and 31 December 2019. Data on patient demographics, APACHE II score, and documented organ failure requiring ICU-level support were abstracted from the RFH ICU's departmental *Intensive Care National Audit and Research Centre* (ICNARC) submission records. Additional data on primary medical diagnosis requiring ICU admission, date of HIV-1 infection diagnosis, HIV-1 RNA viral load (copies/mL), CD4+ T-cell count (cells/mm^3) and date of initial receipt of ART were abstracted from the RFH's *Freenet ICU* (which includes electronic ICU admission notes and discharge summaries), WinPath (CliniSys, Chertsey, UK) blood results systems and from the RFH HIV database. A thorough review of patient electronic health records by two clinicians (MS, RFM) was also conducted to minimise missingness in data abstracted from the multiple data sources.

Variable Definitions

Outcome

The primary outcome was 1-year mortality after ICU admission, regardless of where the death occurred. The time origin of the analyses was index ICU admission date. Follow-up time was right-censored at 365.25 days if the person was known to remain alive at 1 year, or day 7 after ICU discharge if known to be alive at hospital discharge but lost to follow-up. Patients that died on their ICU admission date were assigned a survival time of 0.5 days. We considered only a patient's index, or first, admission during the study period in all data summaries and statistical analyses.

Covariates

We classified patients as having a recent HIV diagnosis if their HIV-1 infection was diagnosed within 3 months prior to ICU admission. We classified a patient as having advanced HIV if their CD4+ T-cell count at ICU admission was <200 cells/mm^3 and/or if they had been admitted to ICU with an AIDS-defining illness. We classified patients as receiving ART prior to ICU admission if: a start date was available that preceded their index ICU admission date at any point; a patient's electronic health record noted ART use prior to ICU admission but no start date was available; and/or HIV-1 RNA was <1000 copies/mL but no start date was available.

Statistical Analysis

Descriptive Analyses

We summarised patient characteristics at ICU admission using frequencies (percentages) for categorical variables and median (interquartile ranges (IQRs)) for continuous variables. We compared patient characteristics at ICU admission between those whose follow-up was censored and those who died within 1-year of ICU admission using Wilcoxon rank sum, Cochran-Armitage, χ^2 and Fisher's exact tests, as appropriate**.** Similar analyses were conducted comparing those with and without a known death status 1 year after ICU admission; and comparing those with and without missing covariate data (see **Supplementary Material**). Overall survival at 1-year was described using the Kaplan-Meier estimate. Between-group differences in 1-year mortality by calendar year of ICU admission (2000-3, 2004-7, 2008-11, 2012-15 and 2016-19) were explored using a Kaplan Meier plot and log-rank test.

Primary Analyses

A Cox proportional hazards model was used to estimate the hazard ratio (HR) to quantify the association between calendar year (as a continuous covariate) and 1-year mortality, and to

explore trends in the 1-year mortality over the study period. Univariable models were used to explore crude associations between 1-year mortality and calendar year as well as several patient characteristics at ICU admission (i.e. age, sex, APACHE II, CD4+ T-cell count ($\log_2$ transformed), recent HIV diagnosis, receipt of ART, respiratory failure and renal failure). In the multivariable Cox model, we adjusted the linear calendar year model for age and sex identified *a priori* as patient characteristics likely to be associated with 1-year mortality, other patient characteristics at ICU admission found to be significantly associated with 1-year mortality in univariable analyses at the 5% level, and recent HIV diagnosis to minimise the potential confounding effect of increased mortality that is observed within the first year of HIV diagnosis.[20] We assessed the proportional hazards for each variable by testing for the inclusion of an interaction between each variable and time using Likelihood Ratio tests.

We conducted analyses as described above restricted to those discharged from hospital (i.e., excluding those who died in ICU/hospital). To account for time in ICU, a left-truncated design was chosen, with the quasi-independence assumption of this design being tested using Tsai's test.[21] Follow-up time was right-censored as described above and the same approach was adopted for variable selection. We also compared patient characteristics measured at ICU admission between those who died in hospital and those who died after discharge to help further explain any discrepancies in effect estimates.

Missing Data

To assess the sensitivity of results to missing data in the covariates included in the primary multivariable Cox model, we conducted random forests imputation under a missing at random assumption and generated 50 imputed datasets.[22] We included all variables in the primary analysis multivariable model. We also included an event indicator for death within 1 year of ICU admission and the Nelson-Aalen estimate of the cumulative hazard.[23]. The final multivariable

Cox proportional hazards regression model for 1-year mortality was fitted to each of the 50

multiply imputed datasets and results combined using Rubin's rules.[24]

All analyses were performed using R version 4.1.0, with two-sided p-values <0.05 considered to

be statistically significant.

Ethics

This project was registered as a Clinical Audit with RFH in July 2020. It was confirmed to be an

Audit by RFH Research and Innovation in October 2021. All data collected were anonymised at

the point of capture.

RESULTS

There were 221 PWH admitted to the RFH ICU over the 20-year study period (72% male, median (IQR) age at ICU admission 45 (38, 53) years). The median (IQR) APACHE II score was 19 (14, 25), 25% had a recent HIV diagnosis, 46% had HIV-RNA $\leq$50 copies/mL, the median CD4+ T-cell count at admission was 122 (30, 297) cells/mm^3, 72% were receiving ART prior to ICU admission, the most common primary diagnosis at ICU admission was lower respiratory tract infection (LRTI) (30%), and the largest proportion of admissions occurred between 2016 and 2019 (29%). For clinical outcomes, the median (IQR) ICU length of stay was 5 (2, 12) days, and cumulative 1-year survival among all patients was 50% (95% confidence interval (CI): 44%-57%) (**Table 1**).

In total, 108 patients died within 1 year, of whom a majority (85/108; 78.7%) died in hospital. Compared to those whose follow-up was censored, these patients had a higher median APACHE II score (24 vs. 15; p<0.001), higher proportion with advanced HIV (80% vs. 56%; p<0.001), lower median CD4+ T-cell count at ICU admission (70 vs. 214 cells/mm^3; p<0.001); and shorter median time interval since HIV diagnosis at ICU admission (1181 vs. 2708 days; p=0.02). These two groups of patients also differed in the distribution of primary diagnosis at admission and ICU admission year, with those who died within 1-year of ICU admission having larger proportions of patients admitted with a LRTI or other infection (p=0.02) and admitted to ICU in the earlier years of the study period (p<0.001) (**Table 1**).

Among patients who died within 1-year of their index ICU admission, the median (IQR) time to death was 12 (3, 40) days; nearly all (92%) of the remaining patients had a follow-up time that was right-censored at 365.25 days. The 9 patients whose follow-up time was right-censored at an earlier point were similar on most patient characteristics to the 104 patients known to be alive

1 year after ICU admission whose follow-up time was right-censored at 365.25 days, but they tended to be younger (median age: 34 vs. 46 years; p=0.02) and were less likely to be receiving ART (25% vs. 75%; p=0.007) (**Supplementary Material**). **Figure 1** presents Kaplan-Meier plots for 1-year of follow-up time overall and by calendar year of ICU admission; the log-rank test indicated strong evidence (p<0.001) that survival patterns differed by calendar year of admission.

In univariable analyses including all patients, patient characteristics at ICU admission associated with 1-year mortality were APACHE II score (crude HR (cHR): 1.10 (95% CI: 1.07-1.13); per unit increase) and CD4+ T-cell count (cHR: 0.83 (0.77-0.90); per doubling in CD4+ T-cell count at admission). Age, sex at birth, recent HIV diagnosis, receipt of ART, respiratory failure and renal failure were not associated with 1-year mortality. The hazard of 1-year mortality decreased over the 20-year study period, with an estimated decrease of 10% per year (cHR: 0.90 (0.87-0.93)). After adjusting for patient characteristics, the estimated decreasing trend in the hazard of 1-year mortality was attenuated to 7% per year (adjusted HR (aHR): 0.93 (0.89-0.98)) and remained statistically significant (**Table 2**). None of the variables violated the proportional hazards assumption in either univariable or the final multivariable models (**Table 3**).

Compared to those who died in hospital, those who died after discharge tended to be living with HIV longer (median: 3388 vs. 818 days; p=0.03), have a lower median APACHE II score (25 vs. 20; p=0.02), and a higher proportion of LRTI and other non-infection-related primary diagnoses at admission to ICU (**Table 4)**. The primary cause of death for the 23 patients that died after discharge included respiratory infection/failure (n=7), carcinoma (3), CNS aspergillosis (2), chronic kidney disease (2), decompensated chronic liver disease (2), multi-organ failure (1), disseminated *Mycobacterium avium* infection (1), and unknown (5).

The Tsai's test indicated no evidence against the quasi-independence assumption (p=0.25); thus, a left-truncated design restricted to those discharged alive using the Kaplan-Meier estimator and Cox models was appropriate. Among those discharged alive, the cumulative 1-year survival was 81% (95% CI: 76%-89%), The log-rank test was consistent with the analysis including all patients (p=0.01; **Figure 2**).

In univariable analyses restricted to those discharged alive, patient characteristics at ICU admission associated with 1-year mortality were APACHE II score (cHR: 1.06 (1.01-1.13); per unit increase), CD4+ T-cell count (cHR: 0.69 (0.58-0.82); per doubling in CD4+ T-cell count at admission), and respiratory failure at ICU admission (cHR: 3.10 (1.31-7.31)). Age, sex at birth, recent HIV diagnosis, receipt of ART, and renal failure were not associated with 1-year mortality. The estimated crude and adjusted HRs for calendar year were consistent with the analyses including all patients. The hazard of 1-year mortality decreased over the 20-year study period, with an estimated decrease of 9% per year (cHR: 0.91 (0.84-0.98)). After adjusting for patient characteristics, the estimated decreasing trend in the hazard of 1-year mortality was attenuated to 8% per year (aHR: 0.92 (0.84-1.02)) (**Table 5**). None of the variables violated the proportional hazards assumption in either univariable or the final multivariable models (**Table 6**).

After multiple imputation for the final multivariable Cox proportional hazards model, findings were consistent with the results summarised above (**Supplementary Material**).

DISCUSSION

We have previously reported a continued improvement in short-term mortality outcomes (in-ICU and in-hospital mortality) in PWH admitted to our ICU.[5] However, data regarding longer-term mortality outcomes in PWH admitted to ICU are limited. To our knowledge, this is one of the largest retrospective observational cohort studies over a 20-year study period to describe 1-year mortality in PWH admitted to ICU in a well-resourced setting, since the establishment of ART as the standard of care for this group.

Our findings show that the rate of 1-year mortality after ICU admission decreased by 10% per year, on average, from 2000-2019. Importantly, whilst the demographics and clinical status of those admitted to ICU has changed over this period, this decrease in mortality was reduced only slightly (7% per year) after adjustment, suggesting that the reduction in mortality is not explained by these changes. These encouraging findings are more likely related to advances in HIV-related clinical care, as well as improvements in care of the critically unwell patient through their ICU stay and post-hospital discharge. Of those who were discharged alive from hospital but died prior to 1 year post-ICU admission, we found a decrease in mortality of 9% per year in univariable analyses, which was attenuated after adjustment for clinical and demographic factors. Our cumulative 1-year survival of 50% is consistent with trends observed in other studies of PWH admitted to ICU, where survival rates of 25-80% at 6 months[8–13] and 25-66% at 12 months[9,10,12,14–18] have been reported. During the 20-year study period, the majority of deaths recorded within 1 year of ICU admission occurred within the index hospital admission; the comparatively small number of deaths that occurred post-hospital discharge and prior to 1 year, is in itself is a reassuring and important outcome to report. This likely reflects a tremendous improvement in the management of HIV both inside and outside the ICU setting. Furthermore, we were able make important distinctions through cause-of-death data between this same

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group and those who survived at 1 year, where AIDS defining-illnesses and ongoing critical organ failure predominate.

With respect to HIV-specific biomarkers, PWH who died within one year of ICU admission had a significantly lower CD4+ T-cell count than those whose follow-up was censored (70 vs. 214 cells/mm^3), consistent with a higher proportion of people with advanced HIV infection (79.8% vs 56.1%). CD4+ T-cell count was also independently associated with 1-year mortality in multivariable analyses for both those who died in hospital as well as those who were discharged alive from hospital but died within 1-year, which is consistent with findings in other studies.[8,17] Taken together, trends in these HIV-specific variables may explain why those who died also had a higher proportion of LRTI (34.3% vs 26.5%) and other infection (15.7% vs 11.5%) as their main admission diagnosis category compared to those with censored follow-up (**Table 1**). AIDS defining-illnesses were heavily represented in LRTI and Other Infection diagnosis categories, where LRTI mainly included *Pneumocystis jirovecii* pneumonia, severe or recurrent bacterial pneumonia and pulmonary tuberculosis, while Other Infection comprised mainly of sepsis. LRTI and sepsis have also been shown to be associated with longer-term mortality in comparable studies; Vargas-Infante et al demonstrated an even longer association of sepsis with 2-year mortality as opposed to 1-year mortality.[1,10,12,14,15,25] LRTI was also the main cause for respiratory failure in our cohort; whilst we did not observe an association for respiratory failure with 1-year mortality when considering all those who died, we did find a univariable association with 1-year mortality when considering only those who survived to hospital discharge but subsequently died within 1 year, suggesting that LRTI and respiratory failure still had a significant role to play in influencing morbidity and mortality when they occurred, albeit as a decreasing proportion of the overall case-load of PWH being admitted to ICU over time.[5]

Given the differences in HIV-specific variables between those who died and those censored, it is interesting that we did not find receipt of ART to be associated with 1-year mortality in univariable analyses. In previous comparable studies, the association of ART with 1-year mortality appears to be inconsistent.[11,14,16,17,25,26] Furthermore, the proportions of recorded ART receipt amongst those who died compared to those censored (72.4% vs. 71.2%) were similar. Unfortunately, we were unable to obtain data with respect to ART adherence for those reportedly established on treatment, or the timing of ART initiation if commenced in ICU and/or after ICU discharge. These missing data may in part explain the difference in HIV RNA viral load and CD4+ T-cell count among those who died and those whose follow-up was censored. To complicate matters further for future work, there is currently no consensus on when to initiate ART in ICU due to legitimate concerns around ART delivery, systemic absorption, drug adverse effects and precipitation of immune-reconstitution syndrome in an already critically unwell patient. However, there exists some data to suggest a benefit to initiating ART during the acute phase of critical illness in ICU.[6,27]

Recent HIV diagnosis (within 3 months of ICU admission) may also have contributed to the significantly lower median CD4+ T-cell count observed in all PWH who died, though it was not shown to be associated with 1-year mortality in univariable or multivariable analyses. We have previously shown 'recent late' diagnosis to be independently associated with increased risk of in-ICU mortality, where 'recent late' diagnosis was defined as presenting with either a CD4+ T-cell count <350 cells/mm^3, or an AIDS-defining illness within the slightly longer period of 6 months preceding an ICU admission.[28,29]

The APACHE II score is a composite measure of physiological derangement calculated in the first 24 hours of ICU admission, currently only validated to predict in-ICU mortality in the HIV-negative population.[30] However, it is widely accepted to be accurate in predicting ICU mortality

in PWH since ART became established as the standard of care. [10,31–35] All PWH who died within one year of ICU admission had a higher median APACHE II score (24 vs 15) compared to those who were censored, though the majority of those who died did so during their index hospital admission (85/108), where their median APACHE II score was higher than those who were discharged alive but subsequently died within 1 year (25 vs 20). This imbalance towards PWH who died during the index hospital admission itself may help to explain why APACHE II score was independently associated with 1-year mortality in multivariable analyses when considering *all* those who died within 1 year, but it was not independently associated with 1-year mortality when considering only those who survived to hospital discharge but subsequently died within 1 year. Our findings support the use of the APACHE II score in predicting in-ICU mortality in PWH and suggest it may have an additional role in predicting in-hospital mortality. Whilst APACHE II has been infrequently observed to be independently associated with long-term mortality in other studies relating to PWH requiring ICU admission, we are unable to draw a similar conclusion based on these findings.[11,16] We used the APACHE II score as this is the pragmatic, standardised approach of UK-based ICUs for the purpose of national centralised data collation and audit. Alternative scoring systems designed to predict in-hospital mortality in ICU patients do exist, such as the Simplified Acute Physiology Score (SAPS), (with updated versions SAPS II and SAPS III available) and is widely used outside the UK setting.[8,36,37] Both scoring systems have been used for PWH admitted to ICU with good effect, and have been studied more recently with a view to formally validating them in this population.[12,17,38,39]

There were several limitations to our study. First, our findings are difficult to apply to other settings, as this was a single-centre, retrospective observational cohort study in the context of a central London teaching hospital where there are well-established HIV and Infectious Disease-specific inpatient services. Second, while our study cohort is one of the largest in the literature with respect to describing long-term outcomes in PWH admitted to ICU, this is still a relatively

small number of patients. Age, sex at birth, recent HIV diagnosis, receipt of ART, sepsis, and in particular, respiratory failure and renal failure, which have been attributed to longer-term mortality outcomes in other studies, had no statistically significant association after adjustment for demographic and clinical factors in our study.[9,10,12,14–18] Third, we were unable to record 1-year mortality outcomes for an ICU comparator cohort of patients without HIV. Fourth, we were unable to capture ethnicity data, which were not routinely recorded by NHS hospitals for most of the study period. Finally, information about tobacco, alcohol or opioid use was not routinely available. The results of our study clearly demonstrate a need for a multi-centre prospective study with matched general ICU admissions to permit identification of better mortality outcomes for PWH admitted to ICU in the ART era. Furthermore, while we were able to capture 1-year outcomes throughout the 20-year study period for almost the whole cohort, we were unable to record the status of those alive at one year, in terms of HIV-related immunosuppression, ART adherence, medical comorbidity or quality of life (using indicators such as the Short-Form (SF)-36 or Karnofsky performance status score).[9] Capturing this data represents an important consideration for future work in all ICU populations, given the expected level of chronic organ dysfunction that might result from surviving acute critical illness, as well as potential comorbidities.

In conclusion, 1-year mortality declined significantly in PWH requiring ICU admission over a 20-year study period. Our findings are confined to a single centre, limiting generalisability, and highlighting a need for a prospective multi-centre prospective UK study with a comparator cohort, where additional data including quality of life indicators following hospital discharge, are captured. Our findings provide additional evidence that HIV status should not play a role in a clinician's choice of patient selection for admission to ICU and highlight the importance of ongoing medical care post-ICU and hospital-discharge.

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Table 1. Summary of patient characteristics, year of admission and clinical outcomes by event status (censored vs. died within 1 year after ICU admission)

Characteristic, n (%) or median (interquartile range)	Overall n=221	Censored n=113	Died within 1 year after ICU admission n=108	p-value
Demographic Factors				
Age (years)	45 (38, 53)	46 (38, 54)	45 (38, 52)	0.71
Male (sex at birth)	158 (71.5%)	83 (73.5%)	75 (69.4%)	0.51
Clinical Factors				
APACHE II score	19 (14, 25)	15 (12, 21)	24 (19, 28)	<0.001
Missing	13	4	9	
Recent HIV diagnosis (≤3 months of ICU admission)	54 (25.1%)	25 (22.3%)	29 (28.2%)	0.32
Missing	6	1	5	
Advanced HIV[1]	143 (67.8%)	60 (56.1%)	83 (79.8%)	<0.001
HIV-related immunosuppression	129			
AIDS-defining infections	57			
AIDS-defining malignancies	23			
Missing	10	6	4	
HIV-RNA ≤50 copies/mL	94 (45.9%)	57 (51.8%)	37 (38.9%)	0.07
Missing	16	3	13	
CD4+ T-cell count at admission (cells/mm^3)	122 (30, 297)	214 (52, 376)	70 (17, 164)	<0.001

Table 1. Summary of patient characteristics, year of admission and clinical outcomes by event status (censored vs. died within 1 year after ICU admission)

Characteristic, n (%) or median (interquartile range)	Overall n=221	Censored n=113	Died within 1 year after ICU admission n=108	p-value
Missing	13	6	7	
Receipt of ART	150 (71.8%)	79 (71.2%)	71 (72.4%)	0.84
Missing	12	2	10	
Time since HIV diagnosis (days)	1988 (65, 4981)	2708 (149, 5937)	1181 (43, 3553)	0.04
Missing	20	7	13	
Primary Diagnosis at Admission Category				
Cardiovascular	7 (3.2%)	4 (3.5%)	3 (2.8%)	0.02
Gastrointestinal	24 (10.9%)	15 (13.3%)	9 (8.3%)	
LRTI	67 (30.3%)	30 (26.5%)	37 (34.3%)	
Neurological	23 (10.4%)	12 (10.6%)	11 (10.2%)	
Oncological/Haematological	19 (8.6%)	4 (3.5%)	15 (13.9%)	
Renal	13 (5.9%)	8 (7.1%)	5 (4.6%)	
Other Infection	30 (13.6%)	13 (11.5%)	17 (15.7%)	
Other[2]	38 (17.2%)	27 (23.9%)	11 (10.2%)	
Year of Admission[3]				
2000-2003	24 (10.9%)	7 (6.2%)	17 (15.7%)	<0.001
2004-2007	43 (19.5%)	9 (8.0%)	34 (31.5%)	
2008-2011	45 (20.4%)	22 (19.5%)	23 (21.3%)	
2012-2015	44 (19.9%)	33 (29.2%)	11 (10.2%)	

Table 1. Summary of patient characteristics, year of admission and clinical outcomes by event status (censored vs. died within 1 year after ICU admission)

Characteristic, n (%) or median (interquartile range)	Overall n=221	Censored n=113	Died within 1 year after ICU admission n=108	p-value
2016-2019	65 (29.4%)	42 (37.2%)	23 (21.3%)	
Clinical Outcomes				
ICU length of stay (days)	5 (2, 12)	5 (2, 12)	4 (2, 12)	0.39
Cumulative 1-year survival (95% confidence interval)[4]	50% (44%, 57%)	--	--	

[1]CD4+ T-cell count <200 cells/mm^3 and/or an AIDS-defining illness at admission. Sub-categories include HIV-related immunosuppression, which describes patients with CD4+ T-cell count <200 cells/mm^3, number of AIDS-defining Infection diagnoses and number of AIDS-defining Malignancy diagnoses within the overall 'Advanced HIV' group.

[2]Includes diagnoses such as post-operative recovery and other non-infection-related primary diagnoses. 23 patients in this group underwent surgery: 15 patients had planned surgery including liver transplant (n=5) and surgical resection of a solid organ tumour (n=6); 8 patients underwent emergency surgery, all of whom underwent laparotomy for management of a hollow viscus perforation.

[3]p-value is based on a Cochran-Armitage test for linear trend using the 4-year groups.

[4]Kaplan-Meier estimate.

Table 2. Results from Cox proportional hazards regression demonstrating factors associated with 1-year mortality after ICU admission, hazard ratio (HR) (95% confidence interval (CI))

	Univariable		Adjusted*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Calendar year of ICU admission (per 1 year increment)	0.90 (0.87, 0.93)	<0.001	0.93 (0.89, 0.98)	0.002
Age (per 5 year increment)	0.97 (0.89, 1.06)	0.47	1.01 (0.91, 1.13)	0.79
Sex				
Female	REF		REF	
Male	0.87 (0.58, 1.31)	0.50	1.35 (0.82, 2.21)	0.23
APACHE II score (per 1 unit)	1.10 (1.07, 1.13)	<0.001	1.08 (1.04, 1.11)	<0.001
Recent HIV diagosis				
>3 months prior to ICU admission	REF		REF	
≤3 months prior to ICU admission	1.24 (0.81, 1.91)	0.32	1.15 (0.70, 1.89)	0.57
CD4+ T-cell count at ICU admission (log$_2$ transformed)[1]	0.83 (0.77, 0.90)	<0.001	0.88 (0.80, 0.97)	0.008
Receipt of ART				
No	REF			
Yes	1.00 (0.64, 1.56)	>0.99	--	
Respiratory failure at ICU admission				
No	REF		--	

Yes	1.32 (0.91, 1.93)	0.15
Renal failure at ICU admission		
No	REF	--
Yes	0.85 (0.44, 1.63)	0.62

[1]The HR can be interpreted as a change in the hazards of 1-year mortality for a doubling in a patient's CD4+ T-cell count at ICU admission.

*Adjusted for linear calendar year, sex, APACHE II, (log_2 transformed) CD4+ T-Cell Count, and recent HIV diagnosis.

Table 3. Results of statistical testing of the proportional hazards
assumption for all variables in univariable models and the final
multivariable Cox proportional hazards model using the Likelihood
Ratio test

	Univariable	Adjusted*
Calendar year of ICU admission	0.73	0.55
Age	0.81	0.60
Sex	0.84	0.43
APACHE II score	0.12	0.13
Recent HIV diagnosis ($\leq$3 months of ICU admission)	0.42	0.43
CD4+ T-cell count at ICU admission (cells/mm^3), log$_2$ transformed	0.15	0.09
Receipt of ART	0.63	--
Respiratory failure at ICU admission	0.16	--
Renal failure at ICU admission	0.92	--

*Adjusted for linear calendar year, sex, APACHE II, (log$_2$
transformed) CD4+ T-Cell Count, and recent HIV diagnosis.

Table 4. Summary of patient characteristics, year of admission and clinical outcomes, comparing those who died in hospital to those who died after hospital discharge

Characteristic, n (%) or median (interquartile range)	Overall n=108	Died in hospital n=85	Died after hospital discharge n=23	p-value
Demographic Factors				
Age (years)	45 (38, 52)	44 (38, 52)	47 (38, 52)	0.58
Male (sex at birth)	75 (69.4%)	59 (69.4%)	16 (69.6%)	0.99
Clinical Factors				
APACHE II score	24 (19, 28)	25 (19, 29)	20 (16, 25)	0.02
Missing	9	7	2	
Recent HIV diagnosis (≤3 months of ICU admission)	29 (28.2%)	25 (31.2%)	4 (17.4%)	0.19
Missing	5	5	0	
Advanced HIV[1]	83 (79.8%)	66 (81.5%)	17 (73.9%)	0.56
HIV-related immunosuppression	129			
AIDS-defining Infection	57			
AIDS-defining Malignancy	23			
Missing	4	4	0	
HIV-RNA ≤50 copies/mL	37 (38.9%)	26 (36.1%)	11 (47.8%)	0.32
Missing	13	13	0	
CD4+ T-cell count at admission (cells/mm^3)	70 (17, 164)	76 (21, 163)	46 (8, 163)	0.34

Table 4. Summary of patient characteristics, year of admission and clinical outcomes, comparing those who died in hospital to those who died after hospital discharge

Characteristic, n (%) or median (interquartile range)	Overall n=108	Died in hospital n=85	Died after hospital discharge n=23	p-value
Missing	7	7	0	
Receipt of ART	71 (72.4%)	53 (70.7%)	18 (78.3%)	0.48
Missing	10	10	0	
Time since HIV diagnosis (days)	1181 (43, 3553)	818 (30, 2837)	3388 (530, 5717)	0.03
Missing	13	12	1	
Primary Diagnosis at Admission Category				
Cardiovascular	3 (2.8%)	3 (3.5%)	0 (0.0%)	0.05
Gastrointestinal	9 (8.3%)	8 (9.4%)	1 (4.3%)	
LRTI	37 (34.3%)	26 (30.6%)	11 (47.8%)	
Neurological	11 (10.2%)	11 (12.9%)	0 (0.0%)	
Oncological/Haematological	15 (13.9%)	13 (15.3%)	2 (8.7%)	
Renal	5 (4.6%)	4 (4.7%)	1 (4.3%)	
Other Infection	17 (15.7%)	15 (17.6%)	2 (8.7%)	
Other[2]	11 (10.2%)	5 (5.9%)	6 (26.1%)	
Year of Admission[3]				
2000-2003	17 (15.7%)	14 (16.5%)	3 (13.0%)	0.21
2004-2007	34 (31.5%)	28 (32.9%)	6 (26.1%)	
2008-2011	23 (21.3%)	18 (21.2%)	5 (21.7%)	
2012-2015	11 (10.2%)	10 (11.8%)	1 (4.3%)	

Table 4. Summary of patient characteristics, year of admission and clinical outcomes, comparing those who died in hospital to those who died after hospital discharge

Characteristic, n (%) or median (interquartile range)	Overall n=108	Died in hospital n=85	Died after hospital discharge n=23	p-value
2016-2019	23 (21.3%)	15 (17.6%)	8 (34.8%)	
Clinical Outcomes				
ICU length of stay (days)	4 (2, 12)	4 (1, 11)	7 (4, 14)	0.09

[1]CD4+ T-cell count <200 cells/mm^3 and/or an AIDS-defining illness at admission. Sub-categories include HIV-related immunosuppression, which describes patients with CD4+ T-cell count <200 cells/mm^3, number of AIDS-defining infection diagnoses, and number of AIDS-defining malignancy diagnoses within the overall 'Advanced HIV' group.

[2]Includes diagnoses such as post-operative recovery and other non-infection-related primary diagnoses. Of 23 patients in this group who underwent surgery, 8 patients underwent 'emergency' surgery; 15 had 'planned' surgery including liver transplant (n=5) and surgical resection of a solid organ tumour (n=6).

[3]p-value is based on a Cochran-Armitage test for linear trend using the 4-year groups.

[4]Kaplan-Meier estimate.

Table 5. Results from Cox proportional hazards regression demonstrating factors associated with 1-year

mortality hazard ratio (HR) (95% confidence interval (CI)), **among those discharged alive**

	Univariable		Adjusted*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Calendar year of ICU admission (per 1 year increment)	0.91 (0.84, 0.98)	0.01	0.92 (0.84, 1.02)	0.12
Age (per 5 year increment)	0.97 (0.80, 1.16)	0.72	0.99 (0.79, 1.23)	0.89
Sex				
Female	REF		REF	
Male	0.77 (0.32, 1.88)	0.57	0.81 (0.30, 2.23)	0.69
APACHE II score (per 1 unit)	1.06 (1.01, 1.13)	0.03	1.03 (0.96, 1.10)	0.45
Recent HIV diagosis				
>3 months prior to ICU admission	REF		REF	
≤3 months prior to ICU admission	0.78 (0.26, 2.29)	0.65	0.54 (0.13, 2.20)	0.39

CD4+ T-cell count at ICU admission (log$_2$ transformed)[1]	0.69 (0.58, 0.82)	<0.001	0.70 (0.56, 0.88)	0.002
Receipt of ART				
No	REF			
Yes	1.16 (0.43, 3.12)	0.77	--	
Respiratory failure at ICU admission				
No	REF		REF	
Yes	3.10 (1.31, 7.31)	0.01	2.70 (0.96, 7.61)	0.06
Renal failure at ICU admission				
No	REF		--	
Yes	1.17 (0.35, 3.96)	0.80		

[1]The HR can be interpreted as a change in the hazards of 1-year mortality for a doubling in a patient's CD4+ T-cell count at ICU admission.

*Adjusted for linear calendar year, sex, APACHE II, (log$_2$ transformed) CD4+ T-Cell Count, recent HIV diagnosis, and respiratory failure at ICU admission

Table 6. Results of statistical testing of the proportional hazards assumption for all variables in univariable models and the final multivariable Cox proportional hazards model using the Likelihood Ratio test, **among those discharged alive**

	Univariable	Adjusted*
Calendar year of ICU admission	0.43	0.56
Age	0.45	0.42
Sex	0.77	0.67
APACHE II score	0.55	0.63
Recent HIV diagnosis ($\leq$3 months of ICU admission)	0.78	0.57
CD4+ T-cell count at ICU admission (cells/mm^3), log$_2$ transformed	0.28	0.85
Receipt of ART	0.25	--
Respiratory failure at ICU admission	0.46	0.32
Renal failure at ICU admission	0.40	--

*Adjusted for linear calendar year, sex, APACHE II, (log$_2$ transformed) CD4+ T-Cell Count, recent HIV diagnosis, and respiratory failure at ICU admission.