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Survival of HIV-infected patients in the intensive care unit in the era of highly active antiretroviral therapy

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Abstract

Background: Several studies describe improved outcomes for HIV-infected patients admitted to the intensive care unit (ICU) since the introduction of highly active antiretroviral therapy (HAART).

Objective: To describe outcome from ICU for HIV-infected patients and to identify prognostic factors.

Methods: Retrospective study of HIV-infected adults admitted to a university-affiliated hospital ICU between January 1999 and December 2005. Information on patient demographics, receipt of HAART, (no patient began HAART on the ICU), reason for ICU admission and hospital course was collected. Outcomes were survival to ICU discharge and to hospital discharge.

Results: One hundred and two patients had 113 admissions to the ICU; HIV infection was newly diagnosed in 31 patients. Survival (first-episode ICU discharge and hospital discharge) was 77% and 68%, respectively; by contrast, ICU and hospital survival among general medical patients was 74% and 65%. ICU and hospital survival was 78% and 67% in those receiving HAART, and 75% and 66% in those who were not. In univariate analysis factors associated with survival were: haemoglobin, Odds Ratio (OR)=1.25 for a 1g/dL increase, 95% confidence interval (CI)=1.03-1.51; CD4 count (OR for a 10-fold increase in cells/μL=1.59, 95% CI=0.98-2.58); APACHE II score, (OR for a 10 unit increase=0.51, 95% CI=0.29-0.90) and mechanical ventilation, (OR=0.29, 95% CI=0.10-0.83).

Conclusions: In this study the outcome for HIV-infected patients admitted to the ICU was good and was comparable with that in general medical patients. Over a quarter of patients had newly diagnosed HIV infection. Patients receiving HAART did not have a better outcome.

Introduction

From the start of the human immunodeficiency virus (HIV) epidemic in the 1980s until the end of 2005, over 78 400 infections had been diagnosed in the UK. While the number of new HIV infections diagnosed annually continues to rise to more than 7 400 per year, the number of HIV-related deaths has remained constant since the introduction of highly active anti-retroviral therapy (HAART) in 1996. In 2005, an estimated 63 500 people were living with HIV infection in the UK [1].

Since 1981, admission rates and intensive care unit (ICU) survival rates have fluctuated in HIV-infected patients requiring critical care support [2]. Early in the HIV epidemic, patients with HIV were deemed incurable. ICU mortality rates were high and long-term survival rates low [3][4][5]. Excluding patients with HIV infection was perceived as justifiable by clinicians. As a direct result of HAART, in populations who are able to access it, there has been a sustained reduction in HIV-associated morbidity and mortality [6][7][8]. HIV infection is now regarded as a chronic disease that may be controlled by HAART when, and if, it is available. Several studies report improved ICU outcomes for HIV-infected patients in the HAART era [9][10][11][12][13[14].

It was our perception that outcomes for HIV-infected patients treated in our ICU were good. We thus performed a retrospective study of all HIV-infected patients admitted to the ICU from January 1999 to end-2005 to identify admission patterns and outcomes in the post-HAART era.

Methods

Patients

Consecutive HIV-infected patients admitted to the ICU at University College London Hospitals (UCLH) between 01 January 1999 and 31 December 2005 were identified. HIV infection was either known or first diagnosed while in the ICU. Patients were identified from manual and electronic searches of hospital discharge summaries of HIV infected patients and cross referenced against the ICU electronic database. Adult patients without known HIV infection admitted to the ICU with general medical conditions between 01 January 1999 and 31 December 2005 were identified from the ICU electronic database; this group of patients

was used to compare outcomes from intensive care. UCLH is a 936 bedded university-affiliated teaching hospital with 22 general ICU beds that provides care for a large population of HIV infected patients. The study was carried out with the approval of the University College London Hospitals Research Ethics Committee.

Data Collection

Demographic information recorded included age, gender, ethnicity and risk factors for acquisition of HIV infection, as well as the patient's awareness of their HIV serostatus on admission to hospital and on admission to the ICU. Patient's receipt of HAART was noted. The final diagnosis made either at the time of death or discharge from the ICU was recorded. Haemoglobin and serum albumin were noted and Acute Physiology and Chronic Health Evaluation (APACHE) II scores on the day of admission to the ICU were calculated. Peripheral blood CD4 counts performed on, or within 4 weeks before the ICU admission were also recorded. At this centre HIV viral load is not normally measured in acutely unwell patients admitted to hospital; nevertheless results were available for some patients. No patient began HAART while on the ICU. The length of the ICU admission, need for mechanical ventilation (and its duration), development of pneumothorax (and whether pneumothorax occurred during mechanical ventilation) were recorded. Outcome was described either as death or survival to discharge from the ICU and to discharge from hospital.

Statistical Analysis

Analysis is based on all 113 patient admissions to the ICU, although because of possible bias from inclusion of multiple admissions from some patients, survival rates are given also for first admissions only. All statistical testing is based on logistic regression, with outcome defined by the groups to be compared, such as survivors and non-survivors and with robust standard errors to acknowledge the multiple admissions from some patients. For duration of ICU admission, duration of mechanical ventilation and CD4 count the log of the value is used in analysis, due to the skewed distribution of these factors. Statistical analysis was performed using Stata version 9 (StataCorp, College Station, Texas, USA). A p value of <0.05 was considered significant.

Results

One hundred and two HIV-infected patients were admitted to the ICU on 113 occasions. Nine patients had two admissions and one patient had three admissions. A median of 15 HIV

infected patients per year (range 10 – 24) were admitted to the ICU. During the study period 1114 HIV-infected patients were admitted to UCLH on 2089 occasions. Characteristics of patients with HIV infection admitted to the ICU are shown in Table 1.

The median (IQR) APACHE II score in the first 24 hours of the ICU admission was 18 (12-23) and the median (IQR) duration of the ICU stay was 3 days (2-9) in those who survived ICU and 8 (3-14) days in those who died in the ICU. Survival to ICU discharge was 77% (79/102) and survival to hospital discharge was 68% for HIV-infected patients with their first admission to the ICU. For all admissions of HIV-infected patients to the ICU survival to ICU discharge was 76% (86/113) and to hospital discharge was 66%.

ICU diagnoses

Lower respiratory tract infection (LRTI) accounted for 48% of admissions and neurological disease for 14% of admissions (Table 2). Of those with LRTI, 43 (80%) had acute lung injury (defined by PaO_2/FiO_2 ratio <40 kPa). The median (IQR) PaO_2/FiO_2 ratio was 17 kPa (13.5-23). The majority with acute lung injury had either *Pneumocystis jirovecii* pneumonia (PCP) (n =25; 58%) or bacterial pneumonia (n =15; 35%). Survival in empirically-diagnosed patients was worse than in those with microbiologically-confirmed PCP. In mechanically ventilated patients, ICU survival and hospital survival was 69% and 63%, respectively. In patients who were not mechanically ventilated ICU survival was 88% and hospital survival was 72%. Eight of 12 patients with pneumothorax had PCP, two had bacterial pneumonia and two had neurological infection. All patients (except one with PCP) were mechanically ventilated when pneumothorax occurred.

The majority of ICU admissions in this HIV-infected cohort were due to community-acquired and opportunistic infections, however sepsis related to chemotherapy administered for treatment of malignancy (lymphoma =3; Castleman disease =1) was responsible for four admissions. The in-ICU mortality in this small group was 50%. Seven admissions (5 patients) resulted from complications of chronic liver disease (variceal haemorrhage =5, hepatic encephalopathy =2) caused by coinfection with hepatitis B and/or hepatitis C. Of these patients 80% died in the ICU.

Diagnoses were HIV-associated in 76 episodes (67%). Patients admitted to the ICU with non-HIV-related diagnoses had higher median CD4 cell counts than those with HIV-related

disease (260 vs 40 cells/μL; p=0.08). This probably reflects the fact that a greater number of those with non-HIV-related diagnoses were receiving HAART (57% vs 28%; p =0.005).

At the time of ICU admission, median (IQR) APACHE II scores, were similar in patients with 16 (11-23) and without 18 (13-23) HIV-related diagnoses, suggesting similar severities of critical illness. Median serum albumin was lower in those with HIV-related disease (23 vs 28 g/L; p=0.001). While the need for mechanical ventilation was identical (62%) among patients with and without non-HIV related illness, the group with HIV-related illness required mechanical ventilation for a longer period (median (IQR) 8 (3-18) vs 2 days (1-6); p=0.002). Similarly, the median (IQR) duration of ICU admission among those who survived was longer in those with HIV-related disease 2 (1-4) vs 5 (3-15) days; p=0.006).

ICU survival was similar in patients with both HIV-related and non-HIV related problems (74% and 81%, respectively; p=0.39). Survival to hospital discharge was not significantly different in those with HIV-related illness (61%), and in those with non-HIV related disease (76%); p=0.15.

Use of HAART

On 42 occasions patients were receiving HAART on admission to the ICU. HIV viral loads were measured in 21 patients and were undetectable in 15, ≤1 000 copies/mL in four patients, and >1 000 copies/mL in two. Median CD4 cell counts were significantly lower in those not receiving HAART (50 vs 150 cells/μL; p=0.02). Distribution of gender, ethnicity and likely route of HIV acquisition were similar in both groups. There was no significant difference in the number of patients requiring mechanical ventilation or in the duration of mechanical ventilation in those who were and were not receiving HAART. Survival to ICU discharge in patients who were (78%) or were not (75%) receiving HAART was similar; p=0.63. Likewise, survival to hospital discharge in those receiving HAART was 67% and 66% in those who were not.

Two patients had immune reconstitution inflammatory syndrome (IRIS) having recently commenced HAART. One, with pulmonary tuberculosis presented with massive mediastinal lymphadenopathy causing stridor, the other, with PCP had IRIS-induced respiratory failure. Two patients had HAART-related lactic acidosis; both were receiving didanosine.

Patients with newly diagnosed HIV infection

Thirty-one patients had newly diagnosed HIV infection. HIV was first diagnosed after hospitalisation, immediately prior to admission to the ICU in 17 patients, in a further 14 HIV infection was diagnosed after ICU admission (Table 3).The most frequently encountered illnesses were PCP (58%) and tuberculosis (13%). Compared to patients with known HIV infection, those with newly diagnosed HIV infection were more immune suppressed, (median CD4 count 20 vs 120 cells/μL; p=0.02), and had a lower serum albumin (median 22 vs 25 g/L; p=0.002). Their ICU admission, if they survived, was also longer (median 6 vs 3 days; p=0.003) and, if mechanically ventilated, required support for longer (median 11 vs 4 days; p=0.003).

General medical patients without known HIV infection

During the study period an additional 1346 patients without known HIV infection and who had general medical conditions were admitted to the ICU on 1484 occasions. Their median (IQR) age =61(36-71) years and median (IQR) APACHE II score was 18 (13-24). The overall length of ICU stay was median (IQR) =2 (1-5) days. Reasons for admission to the ICU were respiratory disease =429 episodes (28.9%) [pneumonia =195, chronic obstructive pulmonary disease =50, acute severe asthma =50, miscellaneous =84], cardiovascular disease =314 episodes (21.2%) [dysrythmias =140, ventricular failure =65, myocardial infarction =58, pulmonary embolus =15, unstable angina =12, miscellaneous =24], neurological disease =184 episodes (12.4%) [status epilepticus =93, intracerebral bleed =23, sub-arachnoid haemorrhage =15, miscellaneous =53], drug/alcohol overdose =149 episodes (10%), gastrointestinal (GI) disease =113 episodes (7.6%) [lower GI bleed =26, oesophageal varices =24, upper GI bleed =23, miscellaneous =40], infection =75 episodes (5.1%) [septic shock =68, miscellaneous =7], metabolic =67 episodes (4.5%) [diabetic ketoacidosis =46, hyponatraemia =18, miscellaneous =3], acute renal failure =50 episodes (3.4%) and miscellaneous =103 episodes (6.9%). Among these general medical patients first episode ICU survival was 74%, and hospital survival was 65%; overall ICU survival was 76% and survival to hospital discharge was 66%.

Predictors of survival in HIV infected patients admitted to the ICU

In univariate analysis, factors predicting survival to ICU discharge were haemoglobin (Odds Ratio [OR] for a 1g/dL increase =1.25, 95% confidence interval [CI] =1.03-1.51, p =0.02), the CD4 cell count (OR for a 10-fold increase in cells/μL =1.59, 95% CI =0.98-2.58, p =0.06),

the APACHE II score, (OR for a 10 unit increase =0.51, 95% CI =0.29-0.90, p=0.02) and mechanical ventilation (OR =0.29, 95% CI =0.10-0.83, p=0.02). Patient's age, gender, ethnicity, HIV risk factor, awareness of their HIV status prior to admission, receipt of HAART, admission to the ICU with an HIV-associated diagnosis, albumin, a PaO_2/FiO_2 ratio >40 and development of pneumothorax were not associated with survival. In multivariate analysis the strength of all associations was reduced and no factors were found significant.

Discussion

In this study of HIV-infected patients admitted to the ICU, survival to ICU discharge and to hospital discharge was 77% and 68%, respectively for first admissions and 76% and 66%, for all admissions; 67% were admitted with HIV- related illnesses.. By contrast, over the same time period (first episode) ICU and hospital survival for general medical admissions to the ICU was 74% and 65% respectively and overall ICU and hospital survival was 76 and 66%, respectively. Although univariate analysis identified that haemoglobin, CD4 cell count APACHE II score and need for mechanical ventilation predicted ICU survival of HIV-infected patients, multivariate analysis showed no factor remained associated with survival, so we do not view any of these four factors as having a dominant association. Two groups with particularly poor survival following admission to the ICU were those with complications of chronic liver disease caused by hepatitis B and/or hepatitis C co-infection, and those with sepsis related to chemotherapy for treatment of HIV-related malignancy. However these groups are small, when compared with all HIV admissions to the ICU and the apparent poor outcome may be similar to that seen early in the AIDS epidemic with management of PCP, before clinicians gained expertise in management of severe disease.

This study found no difference in ICU survival between those admitted with and without HIV-related disease. Over the past decade, anti-retroviral therapy has revolutionised the management of HIV infection, reducing disease progression and improving long-term survival [6][7]. The improvement in survival of HIV-infected patients in the ICU has been ascribed to the availability of HAART [9]. Our data show no evidence that HAART improves either ICU or hospital survival. However, only 37% of patients in this study were receiving HAART on admission to the ICU; among those patients in who HIV viral loads were measured values were undetectable in the majority, and low in the rest, suggesting that these patients were taking HAART and were gaining some immunological benefit. By contrast, 25% of patients were receiving HAART in a study from San Francisco General Hospital

(SFGH) [9]. It is possible that the beneficial effects of HAART are negated by the greater severity of critical illness, as suggested by higher median APACHE II scores (24 versus 16) in our patient cohort, compared with those reported from SFGH [9]. Additionally, differences between our patient group and that from SFGH may explain these contradictory findings. Almost twice as many of our patients (67%) were admitted to the ICU with HIV-attributable disease, by comparison with SFGH (37%). We recently described improved survival of critically ill HIV infected patients in our institution attributable to advances in care of the critically ill, particularly the adoption of protective ventilation strategies [19]. While HAART is undoubtedly effective, it is potentially toxic [15][16][17][18] and may precipitate life-threatening IRIS.

The major limitations of this study are its retrospective nature, the relatively small sample size and acquisition of data from a single centre. Additionally, variability in ICU admission policies over the study period is a further confounder. This is unlikely, as there were no changes in ICU admission policy. While no data are held on HIV-infected patients who were refused admission to the ICU on the grounds of physician-perceived futility, this group is likely to be small.

In the past decade the epidemiology of HIV infection in the UK has changed, with a greater number of cases diagnosed in those born overseas (particularly in sub-Saharan Africa) who acquired infection by heterosexual contact [1]. This is reflected in the change in demographics seen in the HIV-infected population admitted to this ICU since the mid-1990s [20]. The proportion of black Africans has increased from 14.3% to 42.5%, and the number of HIV infections attributable to heterosexual contact from 15% to 50%. Of note, the proportion of admissions related to intravenous drug use has remained constant at 10-11%. Comparison of HIV-infected patients admitted to London ICUs in the mid-1990s [20] with the present cohort shows an improvement in survival rates. A decade ago ICU and hospital survival rates of 67% and 44% were reported [20]; by comparison, in the present study, we report overall ICU and hospital survival rates of 76% and 68%. This improvement is similar to ICU and hospital survival rates of 70-77% and 61-71%, respectively, reported from other centres [9][10] [11][12][13] [21][22]. However, care is needed when making comparisons between institutions, given differences in HIV-infected population demographics, and variations in ICU admission criteria and clinical practice.

We found the most frequent cause of ICU admission was LRTI (48%), complicated by acute lung injury in 80% of cases; PCP was the major cause and outcome was worse in those with empirically-diagnosed infection [19]. While opportunistic and community-acquired infection continues to predominate, the spectrum of disease is evolving. The emergence of HIV-infected patients with end-stage liver disease caused by co-infection with hepatotropic viruses, and those undergoing aggressive chemotherapy for malignancy will in future impact increasingly upon ICU resources. Given the apparent high mortality among this group of patients admitted to the ICU, issues of treatment futility and cost-benefit are germane.

The Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme of 129,647 patients admitted to general ICUs in the UK reported ICU and hospital survival rates of 79.7% and 71.4%, respectively [23]. These data compare favourably with outcomes in our study. The median APACHE II score of the ICNARC group (16.5) was similar to that of our HIV-infected cohort (18), suggesting a similar illness severity [23], although there was a clear age difference (median age 39, vs 63 years in the ICNARC cohort).

In common with studies from several centres in N America and Europe [9][10][11][12[22], HIV infection was first diagnosed in the ICU in a proportion of patients in our study. A recent audit of deaths among HIV-infected adults, carried out by the British HIV Association, identified that >20% of deaths in 2005 were in individuals in who HIV infection was diagnosed too late for effective treatment [24]. These data underscore the need for development of strategies to encourage individuals to undergo HIV testing in order to obviate the need for ICU and its attendant costs.

In the light of the evolution of the HIV epidemic in UK, and its continuing demand on critical care services, it is important to ascertain the cost-benefit ratio of ICU support for critically ill HIV-infected patients. Long-term outcomes for ICU survivors in both quantitative and qualitative terms are vital in guiding such decisions [25]. In a recent study from Paris, survival rates among HIV-infected patients admitted to the ICU in the HAART-era were 85.3% and 70.8%, at 12 and 24 months, respectively [12]. No studies describe longer follow-up for HIV-infected ICU survivors, and none address qualitative issues.

In summary, this study shows that HIV-infected patients admitted to the ICU in the HAART – era have outcomes comparable with those of general medical patients. Over a quarter of

patients had HIV infection newly diagnosed either just before or during ICU admission. Patients receiving HAART did not have a better outcome. Physicians and intensivists should be aware of the complications of HIV infection that may result in admission of HIV-infected patients to the ICU.

Conflict of interest

Professor RF Miller is Co-Editor and Dr AJ Copas is Associate Editor (Statistics) of *Sexually Transmitted Infections*, part of the BMJ Publishing Group.

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Table 1. Characteristics of 102 HIV infected patients admitted to the ICU on 113 occasions from 1999 to 2005

Characteristic	**Number of patients (%)**
Age, years, median (IQR)	39 (32-44)
Male gender	83 (73)
Race, ethnicity	
White	55 (48.7)
Black	48 (42.5)
Asian	4 (3.5)
Other	5 (4.6)
Unknown	1 (0.8)
HIV risk factor	
Heterosexual	54 (50)
MSM	42 (39)
IV drug use	12 (11)
Initial HIV diagnosis	31 (27)
Receipt of HAART	42 (37)
Admission diagnosis	
Non-HIV associated	37 (33)
HIV associated	76 (67)
PCP	28 (25)
Clinical characteristics	
CD4, cells/µL, median (IQR)	75 (10-260)
APACHE II median (IQR)	18 (12-23)
Albumin, g/L, median (IQR)	24 (19-31)
Complications	
Mechanical ventilation	70 (62)
Pneumothorax	12 (11)
Renal replacement therapy	22 (19)

Key: PCP = *Pneumocystis jirovecii* pneumonia, MSM = men who have sex with other men

Table 2. Diagnoses and survival in 102 HIV infected patients admitted to the ICU on 113 occasions.

Diagnosis	**n (%)**	**New diagnosis of HIV infection (n)**	**Receiving HAART (n)**	**ICU survival N (%)**	**Hospital survival N (%)**
Lower respiratory tract infection	54 (48)	24	13	40 (74)	28 (52)
Pneumocystis jirovecii pneumonia[1,2]		18	2	18 (69)	15 (58)
Bacterial pneumonia[3,4]		3	7	11 (65)	9 (53)
Tuberculosis[5]		3	0	7 (100)	6 (86)
Asthma/COPD		0	3	3 (100)	3 (100)
CMV pneumonitis		0	1	1 (100)	1(100)
Neurological problems	16 (14)	5	5	14 (87)	12 (75)
CMV encephalitis[6]	1	1	0	1 (100)	0 (0)
Cerebral toxoplasmosis	3	1	1	3 (100)	3 (100)
Cyrptococcal meningitis	3	1	1	3 (100)	3 (100)
Intra-cranial bleed[7]	3	0	1	2 (67)	1 (33)
Uncontrolled epilepsy	2	0	1	1 (50)	1 (50)
TB meningitis	1	1	0	1 (100)	1 (100)
Bacterial meningitis	1	0	0	1 (100)	1 (100)
HIV encephalopathy	2	1	1	2 (100)	2 (100)
Sepsis[8]	10 (9)	0	5	6 (60)	6 (60)
Post-cardiac arrest	7 (6)	0	5	3 (43)	1 (14)
Post-operative	7 (6)	1	3	7 (100)	7 (100)
Variceal haemorrhage	5 (4)	0	4	3 (60)	2 (40)
HAART-related[9]	3 (3)	0	3	3 (100)	2 (67)
Miscellaneous[10]	11 (10)	1	4	10 (91)	9 (82)

Key: CMV = cytomegalovirus; COPD = chronic obstructive pulmonary disease; IRIS = immune reconstitution inflammatory syndrome; [1] 6 patients were also treated for other opportunistic infections during their admission to the ICU; 3 patients had CMV pneumonitis, 2 patients had pulmonary tuberculosis and 1 patient had CMV encephalitis; [2] 1 patient was re-admitted to the ICU with PCP as a manifestation of IRIS; [3] 1 patient also had cerebral toxoplasmosis; [4] 1 patient was undergoing chemotherapy for non-Hodgkin lymphoma; [5] 2 patients also had PCP and 2 others had CMV encephalitis; [6] 1 also had tuberculous meningitis; [7] 2 patients suffered intra-cranial haemorrhages as a complication of end-stage

chronic viral liver disease; [8]3 patients presented with sepsis without localising features as a complication of chemotherapy for HIV-related malignancies; [9] 2 patients had lactic acidosis and 1 had IRIS; [10] 6 patients had drug overdose, 1 had trauma and 4 had miscellaneous causes .

Table 3. Characteristics of 31 patients with a diagnosis of HIV infection made just prior or subsequent to admission to the ICU.

Characteristic	**Number (%)**
Age, years, median (IQR)	34 (29-41)
Male gender	21 (67.7)
HIV risk factor	
MSM	10 (32)
Heterosexual	20 (65)
IV drug use	1 (3)
Admission diagnosis	
Pneumocystis jirovecii pneumonia	18 (58.1)
Tuberculosis	4 (13)
Bacterial pneumonia	3 (9.7)
HIV encephalopathy	1 (3.2)
CMV encephalitis	1 (3.2)
Cerebral toxoplasmosis	1 (3.2)
Cryptococcal meningitis	1 (3.2)
Thrombo-embolic disease	1 (3.2)
Post-operative	1 (3.2)
CD4 count, cells/μL, median (IQR)	20 (10-60)
Albumin, g/L, median (IQR)	22 (17-28)
APACHE II, median (IQR)	16 (9-22)
Mechanical ventilation	22 (71)
Pneumothorax	8 (26)
Duration of ICU admission, if survived, days, median (IQR)	6 (3-23)
Survived	
to ICU discharge	23 (74)
to hospital discharge	18 (58)