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What determines do-not-resuscitate status in critically ill HIV-infected patients admitted to ICU?

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ABSTRACT

Purpose: To identify factors associated with do-not-resuscitate (DNR) status in critically ill patients infected with human immunodeficiency virus (HIV) admitted to the Intensive Care Unit (ICU) in the era of combination antiretroviral therapy (cART).
Materials and methods: Retrospective cohort study of first-time admissions of HIV-infected patients to ICUs in Edmonton, Alberta, from 2002 to 2014. Multivariable logistic regression analysis was performed to identify factors associated with DNR status.
Results: There were 282 HIV-infected patients with first-time ICU admissions, with an incidence rate of 6.6 per 1000 ICU admissions. Sixty-seven (24%) patients had a DNR designation and support was withdrawn in 37 (13%). In multivariable analysis, APACHE II score (OR 1.13; 95% CI, 1.08–1.19, $p < 0.001$), coronary artery disease (OR 5.70; 95% CI, 1.18–27.76, $p = 0.031$), prior opportunistic infection (OR 2.59; 95% CI, 1.20–5.57, $p = 0.015$) and duration of HIV infection (OR 1.07 per year; 95% CI, 1.01–1.14, $p = 0.025$) were independently associated with DNR status. Ethnicity, HIV risk factors, CD4 count and viral load were not associated with DNR status.
Conclusions: One in four patients had a DNR designation. Illness acuity, selected comorbidity, previous opportunistic infection and HIV duration were associated with DNR designation.

1. Introduction

Historically, intensive care unit (ICU) admission for the management of opportunistic infections (OIs), respiratory failure, and acquired immune deficiency syndrome (AIDS)-related malignancy in patients infected with human immunodeficiency virus (HIV) was associated with very high morbidity and mortality. In fact, previously reported mortality rates in this population were as high as 70% to 90%. [1-3] Because of this, aggressive life-sustaining interventions were often perceived as futile, by clinicians and patients/families. [1,4-7] As a result, admission of patients with AIDS to critical care units was variable by physician/site and even controversial in some jurisdictions. [8,9]

Since the advent of combination antiretroviral therapy (cART) in the late 1990s, however, major advances in HIV care have occurred and outcomes have drastically improved [10-14]. With disease-specific advances, as well as progressive improvement in the delivery of intensive care (e.g., low tidal volume ventilation, sepsis care guidelines), complications and short-term mortality from advanced HIV have decreased sharply [10,12,17-19] HIV has effectively been transformed from a progressive and fatal condition to a manageable and treatable chronic disease. [12,20,21] As HIV-infected patients live longer, non-infectious complications (e.g., atherosclerotic cardiovascular disease and malignancies) and comorbid diseases have increased in frequency and become the drivers of morbidity and mortality. [12,22] The prognosis in critically ill HIV-infected patients also mirrors these changes with substantial improvements in both ICU and hospital survival – approaching survival among the general ICU population. [11,16,23,24]

Hospital admission rates in HIV-infected patients have declined significantly in the cART era; however, ICU admission rates have remained constant or increased. [12,17,18,25,26] In fact, approximately 5 to 12% of HIV-infected patients admitted to hospital require intensive care. Admission diagnoses are no longer dominated by opportunistic infections and HIV-associated malignancies but by sepsis due to common community-acquired pathogens, trauma, overdose, and cardiovascular disease [15]. Of note however, a new diagnosis of HIV and the absence of cART have both been associated with ICU admission. [25-27]

Despite the perception by many that HIV-infected patients should receive equivalent care, the role of critical care in the management of HIV patients remains a point of some debate. [14,20,28] There is a paucity of evidence (e.g., predictive modeling or scoring systems) in the literature to guide both patients and ICU physicians through a rational

Abbreviation: DNR, Do-not-resuscitate.

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decision-making process regarding when to pursue aggressive therapies and when to withhold or withdraw such therapies. [28] While studies have shown dramatic improvement in the survival of critically ill HIV-infected patients in the cART era, our review of the literature to identify factors to aid decision-making in aggressiveness of ICU care and/or do-not-resuscitate (DNR) status in HIV-infected patients did not yield any results. The context around DNR orders in HIV-infected patients also remains unclear - whether they are the wishes of the patient or their surrogate or enacted by the medical team perceived to be acting in the patient's best interest.

Because the factors which may be associated with DNR designation and/or limitations of aggressive organ support in this patient population are not currently known, the purpose of this study was to investigate factors associated with DNR status in critically ill HIV-infected patients admitted to ICU in the cART era.

2. Methods

2.1. Study design, setting and population

This population-based cohort study was conducted in Edmonton, Alberta, Canada, a city with a metropolitan population of approximately 1.4 million people and a large northern catchment area. The city of Edmonton has five closed general medical/surgical ICUs across five hospitals; two academic/tertiary care ICUs and three community ICUs.

We performed a retrospective analysis of a previously established de-identified database. Details of the database and methods of collection have been described elsewhere. [29] Briefly, the database was created in 2016 to describe the epidemiology of critical illness among HIV-infected patients. [29] Patients were identified by electronically cross-referencing ICU admission data with our regional HIV database. Detailed demographic and clinical data on all adult HIV-infected patients admitted to ICU were collected from paper and electronic health records. All first-time adult (age ≥ 17 years) HIV-infected ICU admissions from July 1, 2002 to July 31, 2014, were included in the current analysis.

2.2. Data collection and definitions

Sociodemographic data included age, sex, ethnicity, and HIV disease risk factors. Comorbidity data included alcohol or substance use disorder, cirrhosis, coronary artery disease (CAD), psychiatric illness, chronic obstructive pulmonary disease (COPD), history of malignancy, previous OI [30] and viral coinfection. Hepatitis C virus (HCV) coinfection was defined as HCV RNA positivity or anti-HCV IgG positivity without an available HCV RNA level. Hepatitis B virus (HBV) infection was defined as surface antigen (HBsAg) positivity.

HIV disease factors included the most recent CD4 count (cells/mm^3, percentage [%]) and HIV plasma viral load (PVL, in copies/mL) prior to ICU admission where possible – to minimize any acute changes in CD4 as a result of acute illness. For those patients without CD4 and/or PVL results within 1 year prior to ICU admission, results at the time of ICU admission or at the time of HIV diagnosis (if diagnosed in ICU) were recorded. Those without any available CD4 or PVL results were recorded as missing. To account for changes in assay sensitivity over the study period, a cut-off of <200 copies/mL was used to define suppressed PVL. Where CD4 count and PVL had not been performed during the preceding six-month period, the first CD4 count and PVL performed after ICU admission were used.

Patients who had active cART prescriptions at the time of ICU admission were categorized as being treated with cART, unless the patient was known to be non-adherent to therapy. Non-adherence was recorded only if documented in the patient's chart by the healthcare team (not based on a detectable PVL as this could reflect a number of other factors such as treatment interruptions, malabsorption, drug interactions, or new diagnosis of HIV). cART was defined as an antiretroviral regimen consisting of at least three drugs from two classes. Seroconversion date and duration of HIV infection were recorded. A new diagnosis of HIV was defined as a newly positive HIV serology test during the index hospital admission prior to ICU discharge.

Admission diagnosis was characterized as medical or surgical. We further subcategorized admission diagnosis into respiratory failure, sepsis, trauma, overdose, or other. Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. [31] Illness acuity was captured by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [32] within 24 h of ICU admission. Organ failure/support data included receipt of mechanical ventilation, number of days of ventilation, renal replacement therapy (RRT), and the presence of shock (defined as the administration of vasopressors during the first 24 h of ICU admission for persistent hypotension despite adequate fluid resuscitation). Mortality was reported at 30 days, in ICU and in-hospital.

In cases where patients were transferred between ICUs due to capacity or support limitations, ICU admissions were combined and considered a single admission.

2.3. Clinical outcome and definitions

The *primary outcome* was DNR status. A DNR order is a medical order written by a physician, which instructs health care professionals not to administer CPR if cardiac arrest occurs. A patient with "full code" status has no limitations on their level of organ support, meaning they would undergo interventions such as CPR, intubation and mechanical ventilation, central venous catheters, RRT, and administration of vasoactive medications if necessary. For the purpose of this study, the presence of DNR designation was used as a surrogate marker for limitations in organ support. Other more granular details in addition to DNR status (such as no intubation in the setting of isolated respiratory failure for example) were not recorded. Changes over time in DNR designation were examined by creating two separate 5-year cohorts (early and contemporary). DNR designation by duration of HIV infection (0–30 days, 31 days to 5 years, 5–10 years, and >10 years) was also examined.

2.4. Ethical considerations

The Health Research Ethics Board (HREB) at the University of Alberta approved the study (HREB study number Pro00026353). The requirement for informed consent was waived.

2.5. Data analysis

Demographic characteristics of the cohort were summarized. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile ranges (IQR) where appropriate. Categorical variables were expressed as frequencies and percentages. Continuous variables were compared using the *t*-test or Mann-Whitney *U* test depending on their distributions. The differences between categorical variables were examined using the Chi-square test and, where appropriate, the Fisher's exact test. All *p* values were two-tailed, with statistical significance defined by a p value <0.05. Univariate logistic regression analyses were performed to identify associations with DNR status. Multivariable logistic regression was performed to identify factors independently associated with DNR status. Variables were selected for multivariable logistic regression modeling based on univariate analyses (p-values ≤0.10) and overall clinical significance. All statistical analyses were performed using IBM SPSS Statistics, Version 23.0 (IBM Corp., Armonk, NY).

3. Results

There were 42,632 total ICU admissions to the study ICUs over the study period. Of these, 366 admissions were for 282 distinct HIV-infected patients. Only the 282 distinct first-time ICU admissions were included in our analysis resulting in an incidence of 6.6 per 1000 ICU admissions over the study period. Two academic/tertiary care centers admitted the majority (85%) of cases. [29]

Fig. 1 describes the goals of care designations for the cohort. In total, 210 (74%) patients were full code (i.e., no limitations in support), while 67 (24%) had a DNR designation, meaning they had some documented limitation(s) on organ support. Of these 67 patients, 37 (55%) had withdrawal of life-sustaining therapies. Five patients remained full code throughout their ICU admission until they had life support withdrawn. There were no differences in the proportion of patients with DNR designations over time; 36/138 (26.1%) in the first (early) 5-year cohort and 31/144 (21.5%) in the second (contemporary) 5-year cohort ($p = 0.4$). Those with the shortest duration of HIV (0–30 days; i.e. new diagnoses) had lower rates of DNR status. There were no differences in DNR status beyond 30 days from HIV diagnosis.

3.1. Baseline characteristics

Baseline characteristics according to DNR status are shown in Table 1. Patients were young, with a mean age of 44 (±10) years. A large number of patients (134/282; 48%) were Indigenous and/or HCV co-infected (153/282: 54%). In addition, alcohol and substance use disorders were common (184; 65%). Although CAD frequency was low (10; 3.5%), a higher proportion of patients who had a history of CAD had limitations on support. No significant baseline differences were observed between DNR and full support patients with respect to age, sex, ethnicity, or other comorbidities.

3.2. HIV disease control

The median CD4 count was 125 cells/mm3 (IQR 30–300 cells/mm3), with a median CD4 percentage of 15% (IQR 6–25%) [data missing for two patients]. Median HIV PVL was 28,000 copies/mL (IQR 110–270,000 copies/mL) [data missing for seven patients]. There were no statistically significant differences in the CD4 count or HIV PVL between DNR and full support groups. HIV infection was newly diagnosed in 45 (16%) of patients. Of the forty-five patients with newly diagnosed HIV infection, 41 (91%) had no limitations on support while only five (9%) had DNR designations. There was a history of OI in 90 (32%) patients. Patients with DNR designation were significantly more likely to have a previous

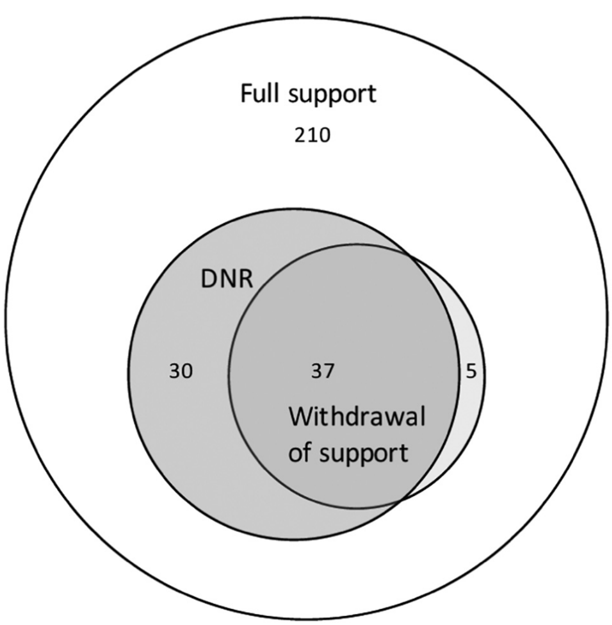

Fig. 1. Goals of care designation for critically ill HIV-infected patients from 2002 to 2014.

Table 1
Baseline characteristics, mortality and univariate analyses.

	Limitations of support			
	All patients	No	Yes	*p* value
Variable	$n = 282$ (100%)	$n = 215$ (76%)	$n = 67$ (24%)	(Chi-square)
Age in years (mean, SD)	44.2 (9.9)	44.1 (10.0)	44.4 (9.2)	0.82
Male sex	169 (59.9)	131 (60.9)	38 (56.7)	0.54
Ethnicity				0.95
Indigenous	134 (47.5)	103 (47.9)	31 (46.3)	0.82
Caucasian	115 (40.8)	88 (40.9)	27 (40.3)	0.93
Black	17 (6.0)	12 (5.6)	5 (7.5)	0.57
Hospital site				0.154
Comorbidities				
HCV coinfection^	153 (54.4)	113 (52.8)	40 (59.7)	0.32
HBV coinfection^	17 (6.0)	12 (5.6)	5 (7.6)	0.55
Chronic lung disease	57 (20.2)	38 (17.7)	19 (28.4)	0.057
Malignancy	21 (7.4)	14 (6.5)	7 (10.4)	0.28
Psychiatric disease	68 (24.1)	56 (26.0)	12 (17.9)	0.17
Cirrhosis	37 (13.1)	28 (13.0)	9 (13.4)	0.93
CAD	10 (3.5)	5 (2.3)	5 (7.5)	**0.047**
Substance use disorder	184 (65.2)	142 (66)	42 (63)	0.61
HIV risk factor				
PWID	169 (59.9)	130 (60.5)	39 (58.2)	0.74
MSM	27 (9.6)	17 (7.9)	10 (14.9)	0.088
Heterosexual	186 (66.0)	140 (65.1)	46 (68.7)	0.593
New diagnosis of HIV	45 (16.0)	41 (19.1)	4 (6.0)	**0.011**
Duration of HIV (years, mean, SD)^	6.0 (5.6)	5.6 (5.5)	7.1 (5.5)	0.067
ARVs at ICU admission	98 (34.8)	72 (33.5)	26 (38.8)	0.43
CD4 count in cells/mm^3 (median, IQR)^	125 (30—300)	130 (40–313)	105 (20–283)	0.23
CD4 percentage (median, IQR)^	15 (6–25)	15 (7–25)	11 (3–25)	0.09
PVL in copies/mL (median, IQR)^	28,000 (110–270,000)	32,500 (110–278,432)	8200 (56–235,000)	0.59
CD4 categories^				0.36
<50	80 (29)	57 (27)	23 (35)	
50–200	87 (31)	71 (33)	16 (24)	
>200	113 (40)	86 (40)	27 (41)	
PVL suppressed^	78 (28.4)	60 (28.6)	18 (27.7)	0.89
History of OI	90 (31.9)	62 (28.8)	28 (41.8)	**0.047**
ICU admission diagnosis				**0.026**
Respiratory failure	10 (3.5)	6 (2.8)	4 (6.0)	0.22
Sepsis	189 (63.8)	133 (61.9)	47 (70.1)	0.22
Trauma	23 (8.2)	23 (10.7)	0 (0)	0.25
Overdose	32 (11.3)	27 (12.6)	5 (7.5)	**0.005**
APACHE II score (mean, SD)	22.1 (7.8)	20.5 (7.0)	27.2 (8.0)	<**0.001**
LDH (median, IQR)^	292 (187–471)	288 (176–463)	324 (225–555)	0.22
Albumin (mean, SD)^	24.3 (7.2)	24.8 (7.3)	22.9 (6.8)	0.06
IMV	213 (75.5)	157 (73)	56 (83.6)	0.079
Shock	133 (47.2)	91 (42.3)	42 (62.7)	**0.004**
AKI/RRT	35 (12.4)	21 (9.8)	14 (20.9)	**0.016**
30-day mortality	55 (19.5)	13 (6.0)	42 (62.7)	<**0.001**
ICU mortality	46 (16.3)	39 (18.1)	56 (83.6)	<**0.001**
In-hospital mortality	70 (24.8)	19 (8.8)	51 (76.1)	<**0.001**

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; CAD, coronary artery disease; PWID, people who inject drugs; MSM, men who have sex with men; ARV, antiretroviral; PVL, HIV plasma viral load; OI, opportunistic infection; ICU, intensive care unit, LDH, lactate dehydrogenase; IMV, invasive mechanical ventilation; AKI, acute kidney injury; RRT, renal replacement therapy.
^Missing data; **bold**, statistically significant.

history of OI (62/215 [29%] full support vs. 28/67 [42%] limitations in support; $p = 0.047$).

The mean duration of HIV infection for patients with a prior HIV diagnosis was 6.0 years (SD 5.5). Of the 237 patients with known HIV infection at the time of ICU admission, only 98 (41%) were prescribed cART at ICU admission. Of those 98 receiving cART, 69 (70.4%) had a suppressed PVL. There were no significant differences between full support vs. DNR groups in duration of HIV or the proportion of patients prescribed cART at the time of ICU admission.

At the time of ICU admission, 22/237 (9%) with known HIV infection did not have CD4 count and/or PVL testing in the preceding six months, suggesting inconsistent engagement in outpatient HIV care prior to ICU admission.

3.3. Critical illness variables and mortality

Most patients were admitted with medical [238 (84%)] vs. surgical diagnoses [44 (16%)]. Sepsis was the most common ICU admission diagnosis (189; 64%). The mean APACHE II score of the population was 22.1 (SD 7.8). Invasive mechanical ventilation (IMV) was received by 213 (76%), 133 (47%) received vasopressor support, and 35 (12%) received RRT during their ICU admission. The median LDH on admission was 292 (IQR 187–471) and the mean albumin level was 24.3 (SD 7.2).

Patients admitted to the ICU with surgical diagnoses or an overdose were less likely to have DNR designations. In fact, 0/44 (0%) of surgical patients has DNR designations. In contrast, patients with a DNR designation had higher APACHE II scores, more likely to have shock and AKI treated with RRT. No significant differences were observed in the diagnosis of sepsis or respiratory failure, or in receipt of IMV.

Patients with DNR designations had higher crude mortality rates (see Table 1).

3.4. Factors associated with DNR status

Factors independently associated with DNR status included CAD (OR 5.7; 95% CI 1.2–27.8; $p = 0.031$), a history of OI (OR 2.6; 95% CI 1.2–5.6; $p = 0.015$), illness acuity (OR 1.13 per 1 point increase in APACHE II score; 95% CI 1.08–1.19; $p < 0.001$), and HIV duration (OR 1.07 per year since diagnosis; 95% CI 1.01–1.14; $p = 0.025$) (Table 2). Other factors such as age, sex, and markers of HIV control were not associated with DNR status. Our multivariable regression model area under the curve test result (C-statistic) was 0.801.

Table 2
Multivariable logistic regression for DNR status.

	Adjusted OR	95% CI	*p* value
Age	0.99	0.95–1.03	0.555
Male	0.78	0.38–1.60	0.493
COPD	2.03	0.92–4.47	0.079
CAD	5.72	1.18–27.76	**0.031**
MSM	2.35	0.81–6.85	0.118
Duration of HIV	1.07	1.01–1.14	**0.025**
PVL	1.00	1.00–1.00	0.857
CD4 count	0.94	0.59–1.51	0.808
History of OI	2.59	1.21–5.56	**0.015**
Admission diagnosis	1.08	0.86–1.34	0.521
APACHE II	1.13	1.08–1.19	<**0.001**
IMV	1.06	0.46–2.49	0.880
Shock	0.89	0.42–1.91	0.773
AKI/RRT	1.82	0.72–4.60	0.208

Adjusted for APACHE II, sex, age, PVL, history of OI, MSM, CAD, COPD, admission diagnosis, IMV, shock, AKI-RRT, duration of HIV, CD4 count. Bold indicates statistically significant. Abbreviations: COPD, chronic obstructive lung disease; CAD, coronary artery disease; MSM, men who have sex with men; PVL, HIV plasma viral load; OI, opportunistic infection; IMV, invasive mechanical ventilation; AKI, acute kidney injury; RRT, renal replacement therapy.

4. Discussion

In this study we describe the characteristics of a cohort of critically ill HIV-infected patients admitted to ICU, compare those with a DNR designation to those with no limitations on aggressive life support therapies, and identify factors associated with the presence of a DNR designation. Not surprisingly, crude mortality rates in patients with DNR designations were significantly higher compared to those who received full support – highlighting the importance of determining predictors of DNR status.

Results to highlight include the relatively young age (mean 44 years) of our patient population and over-representation of specific groups such as Indigenous people, people with HCV co-infection, and people with alcohol or substance use disorder. A detailed description of the overall cohort has been previously published. [29]

Secondly, 24% of critically ill HIV-infected patients admitted to ICU had DNR designations, despite the young age of the cohort. Although we did not case-match to similar non-HIV infected patients, this DNR rate is higher than previously reported in the literature for general ICU populations, where reported incidence of DNR designations ranges from 0.9% to 16.8%. [31-33] These general ICU cohorts were generally older than our cohort with a higher comorbid disease burden. [31-33] DNR status rates in HIV-infected critically ill patients have not been previously reported – providing further relevance to our findings.

When comparing HIV-infected patients with and without DNR designations, the presence of CAD, a history of OI, non-HIV related illness acuity and duration of HIV infection were independently associated with DNR status. Although statistically significant, there were very few patients with CAD (reflected by the wide confidence interval surrounding the adjusted odds ratio) limiting the generalizability of this observation.

Interestingly, markers of HIV disease control, such as CD4 count, PVL or cART prescription were not associated with DNR designation, while history of OI and duration of HIV infection were predictors of limitations in support. Other factors such as age, sex, ethnicity, substance use and HCV co-infection were also not associated with DNR status. Of note, only four of the newly diagnosed HIV patients (6% of newly infected patients) had DNR designations, but this was not significant in multivariable modeling. A review of the literature on factors associated with DNR designation in critically ill HIV-infected patients admitted to ICU did not yield any results. To the best of our knowledge, this is the first study to describe the characteristics associated with DNR status in critically ill HIV-infected patients.

Based on these data, we hope to inform ICU physician practice and goals of care decisions. In our opinion, any limitations in invasive life-support in HIV-patients should be informed by similar prognostic factors as in the general population such as illness acuity and potential reversibility of disease. We do not believe HIV status alone should substantially inform or direct limitations in support. We are pleased that this seems to be the case in our region based on these data.

Despite its strengths, this study has a number of limitations. First, these data are retrospective and observational. Therefore, the study design can only identify associations, and causal inference is not possible. However, these data are fairly comprehensive and outcome data were available for all patients. Second, despite our attempts to perform rigorous risk adjustment, residual confounding may exist as we could not adjust for all potential confounders. Third, some baseline variable data (e.g. LDH, albumin) were missing, which limited our ability to include these variables in our analysis. Fourth, in cases where CD4 was not available in the preceding six months, the first CD4 count measured post ICU admission was recorded – which could be acutely decreased in the setting of critical illness and not necessarily reflective of the underlying degree of immune deficiency. Fifth, accurate data on cART adherence were not available and therefore it is likely that cART adherence was overestimated. Furthermore, an unsuppressed HIV PVL could represent non-adherence, recent cART initiation, resistant virus, drug malabsorption, or drug-drug interactions. Our data are not of sufficient resolution to tease apart these factors. Sixth, although our study included five ICUs, it was restricted to a single large geographic integrated health region; thereby limiting its generalizability. Finally, physician and patient preferences, the timing and specifics of goals of care designation (i.e., pre-hospital, pre-ICU or in ICU; decision made by patient, family or other designate) and reasons for DNR status were not available. We also restricted our study to ICU patients – therefore patients who were not admitted to the ICU for any number of reasons, including perceived futility or pre-existing limitations of care, were not studied. In order to more effectively investigate the reasons behind DNR designations in HIV-infected patients, a prospective study would be needed.

5. Conclusions

In this relatively young, Canadian population-based cohort of critically ill HIV infected patients, one in four patients had DNR status during ICU admission. Illness acuity, the presence of CAD, a history of OIs and HIV duration were associated with DNR designation. Age, sex, ethnicity, substance use or HIV disease severity were not associated with DNR designation. Future work should characterize the timing of patient DNR orders relative to ICU admission and explore patient and clinician-specific factors that may influence DNR status decision-making.

Declaration of Competing Interests

Dr. Anne B Gregory, Dr. Shannon Turvey, Dr. Sean Bagshaw and Dr. Wendy Sligl have no competing interests to declare.

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