Published in final edited form as:

Crit Care Med. 2015 August ; 43(8): 1779–1781. doi:10.1097/CCM.0000000000001053.

HIV-infection and severe sepsis: a bitter pill to swallow

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Keywords

HIV; sepsis; intensive care

Infection with the human immunodeficiency virus (HIV) affects over 1.3 million people in the United States and over 35 million people worldwide.[1] Despite improvements in treatment, HIV is still associated with increased morbidity and mortality. While infectious complications of HIV and the Acquired Immunodeficiency Syndrome (AIDS) have decreased, non-communicable diseases such as cardiovascular disease, chronic obstructive pulmonary disease, end-stage renal disease, and diabetes are becoming more common in HIV-infected persons as they are living longer with highly active antiretroviral therapy (HAART).[2]

The impact of HAART has also been seen in the intensive care unit (ICU) in both the diagnoses seen and their prognoses. In the early AIDS era, mortality for HIV-infected persons admitted to the ICU was very high, and it was often seen as futile to admit these patients to the ICU.[3, 4] HAART, in combination with HIV-specific improvements in care such as corticosteroids for *Pneumocystis* pneumonia and advances in general ICU care such as low tidal volume ventilation, has resulted in an overall improvement in survival of HIV-infected persons admitted to the ICU.[5] Causes of ICU admission have also shifted with a decrease in AIDS-associated diagnoses such as *Pneumocystis* pneumonia; however, respiratory failure has remained the most common cause of ICU admission, and sepsis has increased.[5-8] Additionally, with effective treatment, HIV-infected persons are living longer. In 2009, 36.2% of HIV-infected persons who received medical care were over 50 years old, and this estimate is expected to go over 50% in 2015.[9, 10] Diagnoses common in the ICU setting, such as sepsis, increase drastically with age.[11] Sepsis is also independently associated with worse mortality in HIV-infected persons, even in the era of HAART.[7, 12] Other co-morbid conditions associated with aging with HIV such as cardiovascular disease might also impact mortality in this population. It is unclear if current survival of HIV-infected patients admitted to the ICU with sepsis is as good or worse than HIV-uninfected patients.

In this issue of *Critical Care Medicine*, Cribbs et al. [13] compare baseline characteristics and outcomes in HIV-infected and -uninfected persons admitted to three ICUs in Grady Memorial Hospital with severe sepsis. HIV-infected patients were younger and had a lower body mass index, but they were more likely to have a history of chronic dialysis, pneumonia, infection requiring hospitalization, and sepsis. HIV-infected patients also higher hospital mortality, 50% vs. 38% ($p=0.007$). This association remained significant when controlling for baseline demographics, history of infections, and other predictors of mortality, including the Acute Physiology and Chronic Health Evaluation (APACHE) II score which was available in a subset of HIV-infected and -uninfected persons. While the primary source of infection was most commonly respiratory in both HIV-infected and -uninfected individuals, respiratory was more often the primary source in HIV-infected, 61% vs. 48% ($p=0.002$); and HIV-infected persons were less likely to have gram-positive infections (39% vs. 53%, $p=0.01$), but more likely to have fungal infections such as *Pneumocystis*, *Cryptococcus*, and *Candida* as the primary cause of their sepsis. The difference in outcomes with HIV infection may be related to subtle immune defects even in treated HIV or other underlying factors that remain as unadjusted confounders.

A striking finding of the study was that even in a major US city, the population had a low prevalence of HAART use at the time of severe sepsis (22%), and most participants had a CD4 count ≤ 200 (79%). Only 11% of HIV-infected participants were new diagnoses of HIV. The distribution of CD4 count was low, even in those on HAART. It is hard to know how outcomes of severe sepsis in HIV-infected persons well-controlled on HAART might differ from that found in this study and caution should be taken when applying results from this study to different ICU populations. Additionally, while HIV treatment is widely available in the Ponce de Leon Center in Atlanta, Georgia, where most HIV-infected participants in this cohort seek care, there is a disparity in health care coverage that likely confounds the relationship between HIV infection and in-hospital mortality in this study. The study also does not elucidate how longer term outcomes may differ between HIV-infected and -uninfected person after severe sepsis, which may be of even greater divergence considering the pre-morbid conditions and potential differences in access to care.

Cribbs et al. show us that outcomes in HIV-infected patients admitted to the ICU with severe sepsis are worse than outcomes in HIV-uninfected patients. These data point out the need to improve HIV care and care delivery, both in the acute intensive care unit setting (awareness of the spectrum of infectious causes) and potentially in chronic HIV care delivery. The study has generated questions worth answering to determine why HIV-infected persons have worse outcomes from severe sepsis.

Acknowledgments

Copyright form disclosures: The authors received support for article research from the National Institutes of Health.

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