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Review Article

Interactions between HIV Infection and Sepsis among Critically Ill Patients: A Systematic Review

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Abstract

The epidemiology of critically ill human immunodeficiency virus (HIV)-infected patients admitted to intensive care units (ICU) dramatically changes since the advent of highly active antiretroviral therapy (HAART). Currently, non-Acquired Immunodeficiency Syndrome (AIDS) illnesses are responsible for the majority of admission on ICU, contrasting with pre-HAART era, where AIDS as well as opportunistic infections (OI) dominated. In this context, sepsis has emerged as a leading condition mandating hospitalization and being associated with worse prognosis. However, data with respect to prevalence of sepsis, causative OI, outcome, and the influence of HAART on sepsis are scanty on literature. Three databases were searched for publications reporting the prevalence of HIV-associated sepsis in post-HAART era. Thirty-three studies were included for review. The prevalence of sepsis ranged from 2%-62%. *Pneumocystis jirovecii pneumonia* was the most common OI. Sepsis was much prevalent and associated with higher mortality in HIV group. HAART did not influence sepsis outcomes. Our findings show that HIV increased the risk of sepsis and contributes to a higher mortality in HIV critically ill patients. Further studies are urgently needed to assess the optimal management strategies of HIV-associated sepsis.

ABBREVIATIONS

HIV: Human immunodeficiency virus; **AIDS:** Acquired immune deficiency syndrome; **HAART:** Highly active antiretroviral therapy; **ICU:** Intensive care unit; **OI**: Opportunistic infections; **PJP**: *Pneumocystis jirovecii* pneumonia (PJP)

INTRODUCTION

HIV infection is a complex disease that often involves intensive care support. The rapid expansion of highly active antiretroviral therapy (HAART) programs has dramatically shifted the epidemiology paradigm of HIV-infected patients admitted to intensive care units (ICU). If on pre-HAART era, traditional Acquired Immunodeficiency Deficiency Syndrome (AIDS)-associated events were responsible for the majority of ICU admission, during current HAART era, non-AIDS conditions contribute substantially for ICU admission and mortality [1]. More importantly, sepsis emerges as a leading indication that mandates ICU hospitalization in HIV-infected subjects [2].

Several disparities exist with respect to sepsis in critically ill HIV patients. Immune perturbations commonly seen in advanced stage of infection render infected hosts more susceptible to infection as well as bacterial sepsis. Further, infected individuals are at higher risk of hospitalization and less likely to be admitted in ICU for sepsis compared with HIV-uninfected patients [2-4].

We previously had review the clinical presentation, immune-inflammatory features and prognosis related to sepsis in HIV-infected patients [2]. However, the lack of standardized diagnostic criteria, as well as disparate study populations evaluated (community-acquired sepsis versus nosocomial sepsis patients) and research methods used, have led to conflicting data regarding the true prevalence of sepsis among critically ill HIV-infected subjects during current HAART period [5,6]. Thus, we aim to systematically assess the prevalence of sepsis over HAART period in HIV-infected patients admitted to ICU. In addition, we describe the main opportunistic infections (OI) associated with HIV infection in contemporary era, outcomes of sepsis, risk factors and the influence of HAART on sepsis outcomes.

METHODS

Search strategy

This review was done according to PRISMA guidelines [7]. Initially, we searched PubMed, Web of Knowledge and Scopus databases from December 1996 until April 31, 2014 for eligible articles, using the following search terms and Boolean operators: " HIV" OR "Human immunodeficiency virus" OR "AIDS" AND "sepsis" OR "septic shock" OR "SIRS" AND "critical care" OR "intensive care". Searches were updated by JASM on 1 April 2015. Reference lists of all records included were screen for potentially studies. No language restrictions were imposed. Our primary outcome of interest was the prevalence of sepsis among critically ill HIV-infected patients admitted to ICU in post-HAART era. The latter was defined as antiretroviral period that initiated from December 1996 onwards, to coincide with the introduction of protease inhibitor HIV drug class in clinical practice.

Study selection

Studies were considered eligible if: (1) involving adult HIV-infected patients; 2) admission to ICU service; (3) admission during current HAART era; (4) reported prevalence of sepsis among persons living with HIV, according to latest sepsis definitions [8]. The following criteria were used as exclusion: (1) involving pediatrics or pregnant women populations; (2) animal or experimental studies and finally (3) reporting prevalence of sepsis in pre-HAART era.

Three reviewers (JASM, RA, HA) independently assess studies eligibility. Data were double-checked by AMJ for all included articles. Disagreement between reviewers was resolved by consensus or in consultation to senior author AMJ. We did not contact authors for further information or confirm the accuracy of information included in our review with the original researchers. No studies were excluded on the basis of quality.

Data extraction

Data was extracted with respect to first author, year of publication, study design, study location, time frame, sample size, $CD4^+$ count, prevalence of sepsis among critically ill HIV-infected subjects, hospital mortality, and mortality directly attributed to sepsis and prevalence of main opportunistic pathogens at ICU admission.

RESULTS

Our initial literature search yielded 829 records, of which thirty-three met the inclusion criteria and were taken through for full paper review. Reasons for exclusion are showed in figure 1. All articles were published in English. Ten studies took place in United States of America; 7 in France; and sixteen in other parts of the world. All studies were observational in design. In total 20.137 HIV-infected patients data were analyzed. The reporting period ranged from the end of 1996 to 2013. The patient's median $CD4^+$ cell count at ICU admission was ≤ 200 cells/μl in twenty-four studies. Summary of study characteristics are presented in Table 1.

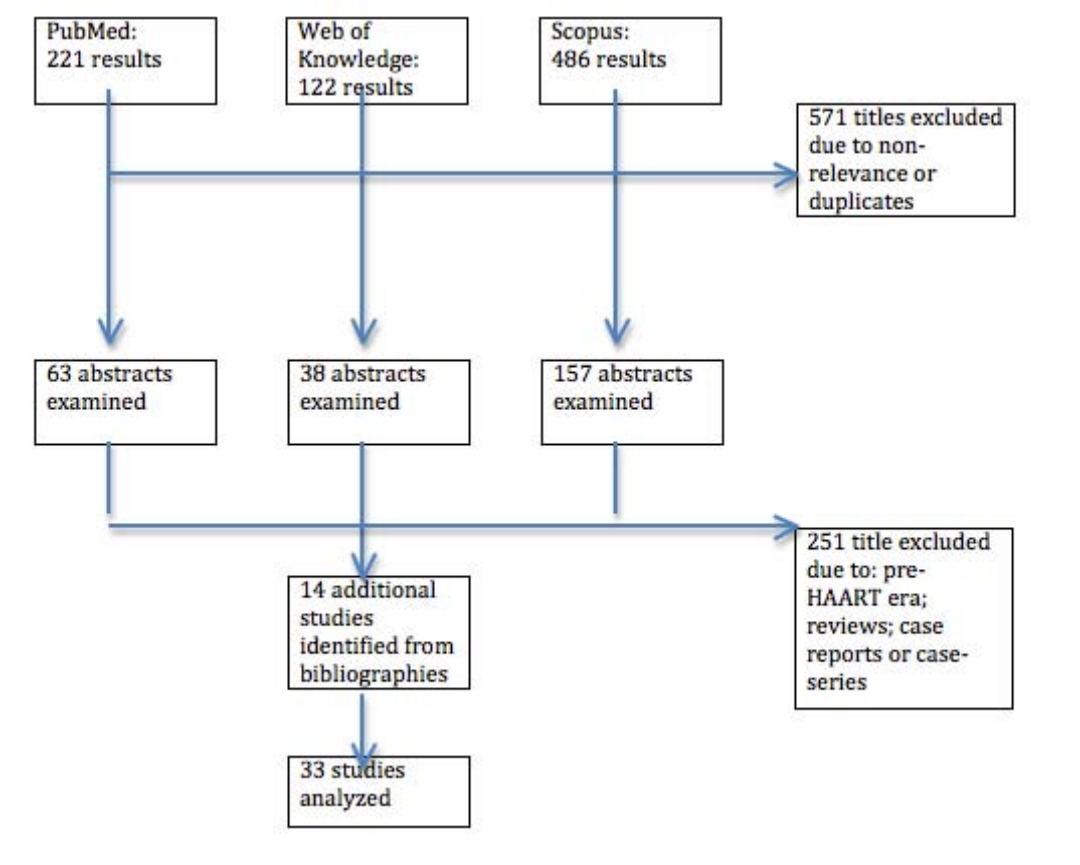

Figure 1 Search strategy and papers selection flowchart.

Prevalence of Sepsis in HIV-Infected Patients Admitted To ICU during HAART Era

The prevalence of sepsis varied between 2% and 62% with the exception of 1 study that had 100%, which can be attributed to the fact that patients selected for the study were mainly those with signs of HIV-associated sepsis. No meta-analysis could be conducted due to insufficient data and clinical heterogeneity of the included studies.

Three studies compared the prevalence of sepsis according to HIV serology. Medrano et al. reported a prevalence of 57.75% versus 39.41% in HIV-infected and uninfected, respectively ($p<0.001$) [10]. Akgun et al. estimated a prevalence of 10% and 4% in HIV-infected and uninfected patients, respectively ($p<0.05$) [13]. Finally, Cobos-Trigueros et al. estimated 36% of prevalence in infected individuals compared to 16% in control group ($p<0.0001$) [15].

Table 1: Summary of selected studies evaluating prevalence of sepsis in HIV patients admitted to ICU in HAART era.

Author, year, [reference]	Study Location and time frame	Study design	No. HIV+ patients	Median CD4+ count on ICU admission (cells/mm^3)	Prevalence of Sepsis (%)	Hospital Mortality (%)
Barbier, 2014 [9]	France, 1999-2010	Multicenter ROS	6,373	N/A	19.3	26.9
Medrano, 2014 [10]	Spain, 2005-2010	Multicenter ROS	1,891	N/A	58	67.9
Amancio, 2013 [11]	Brazil, 2008-2010	Multicenter POS	30	70	50	50
Orsini, 2013 [12]	USA, 2011-2013	POC	42	123	41	31
Akgun, 2013 [13]	USA, 2002-2010	Multicenter POS	539	278	10	19
Silva, 2013 [14]	Brazil, 2006-2008	POS	36	25	62	56
Cobos-Trigueros, 2013 [15]	Spain, 2006-2008	POS	64	200	36	28
Amancio, 2012 [16]	Brazil, 2006	ROS	125	116	20	68
Foo, 2012 [17]	Australia, 1999-2005	ROS	24	150	15	46
Greenberg, 2012 [18]	USA, 2006-2009	ROS	120	30	100	42
Meybeck, 2012 [19]	France, 2000-2009	ROS	85	112	11	N/A
Morquin, 2012 [20]	France, 1997-2008	Multicenter ROS	98	173.5	11	12
Chiang, 2011 [21]	Taiwan, 2001-2010	ROS	135	30	33	49
Adlakha, 2011 [22]	UK, 1999-2009	POS	192	110	11	30
Turtle, 2011 [23]	UK, 2001-2006	ROS	43	128	28	51
Van Lelyveld, 2011 [24]	Netherlands, 1996-2008	ROS	80	83	15	45
Japiassú, 2010 [25]	Brazil, 2006-2008	POS	88	75	20	49
Coquet, 2010 [26]	France, 1998-2005	ROS	284	92	24	N/A
Mendez-Tellez, 2010 [27]	USA, 2004-2007	Multicenter ROS	66	N/A	6	44
Barbier, 2009 [28]	France, 1996-2006	ROS	147	192	37.8	19.7
Croda, 2009 [29]	Brazil, 1996-2006	ROS	278	39	31	N/A
Powell, 2009 [30]	USA, 2000-2004	ROS	281	109	20	31
Palepu, 2008 [31]	Canada, 1999-2006	Multicenter POS	309	N/A	21	39
Vargas-Infante, 2007 [32]	Mexico, 1985-2006	ROS	53	257	26	N/A
Dickson, 2007 [33]	UK, 1999-2005	ROS	102	75	9	32
Palacios, 2006 [34]	Spain, 1996-2003	ROS	49	195	2	53
Khouli, 2005 [35]	USA, 1997-1999	Multicenter ROS	259	85	13	39
Mrus , 2005 [3]	USA, 1999	Multicenter ROS	7,638	N/A	10	29
Narasimhan, 2004 [36]	USA, 2001	POS	63	N/A	16	29
Vincent, 2004 [37]	France, 1998-2000	ROS	236	N/A	28	30
Casalino, 2004 [38]	France, 1997-1999	POC	230	134	23	N/A
Morris, 2002 [39]	USA, 1996-1999	ROC	295	64	12	29
Afessa, 2000 [40]	USA, 1995-1999	POS	141	148	15	N/A

Data from samples, median CD4+ count, prevalence of sepsis and hospital mortality were extracted only for subjects included in post-HAART era
N/A denotes not available
ROS retrospective observational study; POS prospective observational study

Causative Opportunistic Pathogens in Critically Ill HIV-Infected Patients

When analyzing all studies in aggregate, *Pneumocystis jirovecii* was the most common opportunistic organism in HIV patients admitted to ICU, followed by *Mycobacterium tuberculosis, Toxoplasma gondii,Cytomegalovirus,* and *Cryptococcus neoformans* (Table 2).

Outcome of Sepsis in Critically Ill HIV Patients

Sixteen studies reported on sepsis-associated mortality among HIV patients. Data on mortality rates are summarized in Table 3.

Nine studies identified sepsis diagnosis as an independent predictor of ICU, hospital and long-term mortality. Sepsis increases up to 26-fold the odds of mortality in critically ill HIV subjects (Table 4).

Reported factors associated with fatal outcomes in HIV septic patients were mainly related to degree of disease severity. However, information on this topic was limited, and only available in 2 selected studies. Amancio et al. found that increased age (OR 1.05, CI 95% 1.02-1.09, p=. 002) and IL-6 serum levels were significantly associated with hospital mortality in HIV septic shock patients [11]. Conversely, Greenberg et al. found that in-hospital mortality of septic HIV patients was associated with higher APACHE II and SOFA scores, need for mechanical ventilation, and vasopressor support [18].

HIV is a Risk Factor for Mortality Due to Sepsis

Four studies reported on the impact of HIV infection on sepsis-associated mortality [3,10,13,14]. All studies documented a statistical significantly increase ICU mortality in HIV septic patients compared to uninfected patients. One of these, a Spanish retrospective cohort study, demonstrated an increase cumulative mortality rate in HIV patients at day 7, 30 and 90 [10].

Influence of HAART on Sepsis Outcome

Out of the thirty-three studies included, 6 reported HAART administration as independently predictor of survival in multivariate analysis [16,20,22,29,32,38]. These studies reported a protective effect of HAART receipt in both treatment naïve and experienced patients. Of note, this effect was observed in 6-month as well as 24-month time frame after ICU discharge.

Table 2: Overview of the prevalence of different opportunistic pathogens in HIV patients admitted to ICU.

Pathogen	Prevalence (%)
Pneumocystis jirovecii	17[a]
Mycobacterium tuberculosis	11,4[b]
Toxoplasma gondii	7[c]
Cryptococcus neoformans	3,7[d]
Cytomegalovirus	4,2[e]

Percentages were obtained by analyzing in aggregate all studies that reported on each specific opportunistic pathogen

a. Sources: [all studies except references 3,11, and 31]
b. Sources: [9, 10, 11, 14, 16, 18, 19, 20, 22, 23, 25, 28, 29, 33, 37, 38]
c. Sources: [9, 10, 16, 18, 19, 20, 22, 23, 26, 28, 29, 33, 34, 37, 38]
d. Sources: [9, 10, 11, 12, 14, 15, 16, 17, 18, 20, 22, 26, 28, 29, 33, 38]
e. Sources: [9, 10, 11, 15, 16, 18, 20, 21, 22, 28, 29, 33]

Table 3: Studies evaluating sepsis-associated mortality in HAART era.

First author, year	Study Location and Time frame	Sepsis-associated mortality
Medrano, 2014	Spain; 2005-2010	73.8%¶
Amancio, 2013	Brazil; 2008-2010	50%
Orsini, 2013	USA; 2011-2013	61.5%
Silva, 2013	Brazil; 2006-2008	55.6%
Morquin, 2012	France; 1997-2008	14%
Turtle, 2011	UK; 2001-2006	33%
Coquet, 2010	France; 1998-2005	64.1%§
Japiassú, 2010	Brazil; 2006-2008	66%§
Mendez-Tellez, 2010	USA; 2004-2007	10%
Vargas Infante, 2007	Mexico; 1985-2006	76%§
Dickson, 2007	UK; 1999-2005	40%
Khouli, 2005	USA; 1997-1999	50%
Mrus, 2005	USA; 1999	29%[a]
Narasimhan, 2004	USA; 2001	40%
Vincent, 2004	France; 1998-2000	66%¶
Afessa, 2000	USA; 1995-1999	82%¶

¶ Refers to Severe Sepsis
§ Refers to Septic Shock

Table 4: Studies reporting sepsis as major independent predictor of mortality in HIV patients admitted to ICU.

First Author, Year	In-ICU mortality			
	n¶	OR (95% CI)	95% CI [range]	*P*
Medrano, 2014	1.092	1.44	1.30-1.59	0.05
Akgun, 2013	55	26.8	5.25-137	0.01
Amancio, 2012	25	4.38	1.78-10.76	0.05
Chiang, 2011	45	2.91	1.11-7.62	0.029
Coquet, 2010	68	3.67	1.53-8.80	0.004
Japiassú, 2010	44	3.13❖	1.21-8.07	<0.01
Croda, 2009	87	3.16	1.65-6.06	0.05
Vargas-Infante, 2007	21	2.4❖	1.1-5.2	0.02
Mrus, 2005	7.638	2.41	2.23-2.61	0.05

¶ Number of patients admitted with HIV-associated sepsis
❖Values are given as hazard ratio (95% confidence interval)
95% CI denotes confidence interval; ρ value<0.05 is considered statistically significant

DISCUSSION

In our systematic review, we initially assess the prevalence of sepsis among HIV-infected patients admitted to ICU in post-HAART era. We found that the prevalence of sepsis in this critical population varies between 2-62%. In accordance with other studies, our results show that sepsis represents an important non-AIDS related illness in HAART-treated individuals [41]. A substantial increment in sepsis prevalence was also noted

in current era corroborating with previous studies, which documented a prevalence of 15% in pre-HAART period [42].

In addition, we found that HIV subjects had a significantly increased risk of developing sepsis compared to uninfected subjects. A combination of factors might explain the increased susceptibility to infection in this patient group. For instance, HIV-induced immune perturbations, low CD4/CD8 ratio and the residual immune dysregulation syndrome are some of the factors that had previously been described to be implicated in the pathogenesis of HIV-associated sepsis [4,43,44].

The natural history of HIV infection has changed dramatically after the introduction of HAART. However, we demonstrate that OI still represent a major cause of morbidity in HIV patients admitted to ICU during current HAART era. For this reason, physicians caring for septic HIV patients must always consider OI as potential causes of sepsis.

Pneumocystis jirovecii pneumonia (PJP) was the most common OI during ICU admission, with a prevalence of 17%. Considering only studies from resource-constrained settings with higher burden of HIV infection, the prevalence rises to 23%. Therefore, PJP should also be suspected in every HIV septic patient with respiratory failure.

Mortality rates associate with sepsis vary greatly between studies, probably due to differences with respect to the degree of severity of sepsis. As expected, studies that included septic shock HIV patients reported higher mortality rates compared with studies that refer to sepsis or severe sepsis. Conversely, We hypothesized that such differences could be explained by regional differences regarding the management of HIV critically ill subjects. For example, studies done in resource rich settings had lower sepsis mortality compared to ones done in Brazil or Taiwan.

The median in-hospital mortality observed in our study was 39%, contrasting with 70% observed in pre-HAART era [1]. Current evidence does suggest that factor unrelated to HIV infection do play a role for the improved survival in this patient population. Miller et al. reviewed a cohort of fifty-nine PJPHAART-naive patients admitted to ICU, and observed a marked reduction in mortality throughout the years (from 71% to 34%) independently of HAART uptake [45]. They identified the year of diagnosis of infection, age, need for mechanical ventilation and development of pneumothorax as predictors factors related to mortality, and concluded that the general improvement in the provision of critical care might play a role in improving outcomes of HIV-infected subjects admitted to ICU. These data are consistent with our analysis, which only identified 6 studies where HAART administration had a protective effect on survival. Taken together, these data call for further confirmation on the benefit of HAART use in critically ill HIV patients.

Our study has several limitations. First, all studies included in this review are observational, which will have a high publication bias compared to randomized controlled trials. As a result, a publication bias for this review should be strongly considered. Second, We found few reports from high HIV-burden settings, where the prevalence of sepsis might be different from that observed in our study, which included most data from low HIV-burden settings. Third, there may be a selection bias with respect to the prevalence of opportunistic pathogens founded, as selected publication do not report detailed etiologies of opportunistic diseases. In addition, we could not stratify the prevalence of opportunistic pathogens according to geographical regions (Americas, Europe, Africa), because the majority of studies included were done in France and USA. Fourth, the prevalence's of HIV–associated sepsis found in our review should not be considered entirely representative of country estimates, as few studies were multicenter. Finally, we hypothesized that there were a bias regarding the difference in prevalence of Sepsis according to HIV status. Studies that found no difference may be less likely to stratify their results by HIV status.

Several issues merit of further investigation was identified. Although no treatment guidelines regarding Sepsis and HIV coinfection had been identified, it is anticipated that the current Surviving sepsis campaign does not completely address this especial population in detail, because most of the studies cited in the latter guideline excluded HIV positive patients [46]. For this reason, the recommendations cannot be automatically extrapolated to HIV population. Afterwards, we suggest that HIV counseling and testing should always be performed in patient admitted to ICU, as we have showed an increased risk of sepsis as well as higher sepsis related mortality in infected group compared to uninfected patients. Lastly, the role of simplified HAART regimens (i.e. Protease inhibitor monotherapy) in HIV patients with several sepsis-associated organ injuries remains to be clarified [47].

In conclusion, the evidence that is available and is presented in this review show that sepsis is an important cause of morbidity and mortality in critically ill HIV patients during HAART era. In addition, HIV infection increased the risk of developing sepsis and contributes to a higher mortality in infected subjects. Finally, our findings highlight the urgent need for research on the impact of HAART uptake on HIV-associated sepsis.

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