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# The Outcome of HIV-Positive Patients Admitted to Intensive Care Units with Acute Kidney Injury

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## 1. Introduction

Acute kidney injury is a serious clinical problem with significant morbidity and mortality. Several factors are recognized to aggravate the outcome including advanced age, gender, oliguria and the serum creatinine level. What is currently unknown is whether the presence of the human immunodeficiency virus (HIV) aggravates the outcome of patients who develop acute kidney injury (AKI). Sub-Saharan Africa currently bears the brunt of the global HIV pandemic. In South Africa alone more than 5.7 million people are infected ((UNAIDS 2008 report on the global AIDS epidemic, 2009), creating substantial additional pressure on already inadequate social and healthcare infrastructures. Acute kidney injury occurs commonly in HIV-infected patients admitted to hospital and carries with it substantial mortality. In a resource-poor environment clinicians are often forced to select patients with a better chance of survival for admission to the intensive care unit (ICU). A rigorous evaluation of the outcomes of HIV-positive patients admitted to ICU with AKI may assist in identifying factors associated with better survival, and thus aid in the cost-effective management of these patients.

## 2. Description of the conditions involved

### 2.1 Acute kidney injury

Acute kidney injury is characterized by a sudden reduction in glomerular filtration rate and is expressed clinically as azotemia with or without accompanying oliguria. Research on the outcomes of patients with AKI has been hampered by the absence of uniformity in the definition of the condition. With more than 35 different definitions being used before 2002, clinicians battled a bewildering array of reports varying in severity and mortality rates for patients (Ronco et al, 2010). In order to create some uniformity, the Acute Dialysis Quality Initiative formulated a consensus definition, the RIFLE criteria which were published in 2004. In a subsequent review, The Acute Kidney Injury network (AKIN) proposed minor modifications to the RIFLE system. This included the use of the term *acute kidney injury* instead of *acute renal failure*, recognizing that kidney injury does not always result in failure or the need for renal replacement therapy, but that even minor injury can have severe consequences, especially in severely ill patients, including HIV-infected patients.

The mortality of AKI remains high and is of the order of 50% in hospitalized patients who require dialysis (Metcalf et al, 2002). ICU patients with multi-organ failure have mortality rates approaching 90%, despite improvements in the management of these patients (Uchino et al, 2005).

AKI is common in HIV-infected patients admitted to hospital, with a published occurrence rate of 5.9 per 100 person years in developed countries (Franceschini et al, 2005). More than 50% of episodes are attributed to infection. Most patients have pre-renal failure, often resulting in acute tubular necrosis from sepsis and fluid depletion because of vomiting, diarrhea and poor intake (Williams et al, 1998). There are little reliable data available on the causes and incidence of acute HIV-related kidney injury in Africa, but it is clear that a different pattern of presentation from the developed world is observed. Patients are frequently previously well young black adults who present with overwhelming opportunistic infections. In a Cape Town-based study this has led to a 500% escalation in the provision of acute dialysis to HIV-infected patients over a 6 year period (Arendse et al, 2011). This study found acute tubular necrosis as the clinical and biopsy-determined cause for AKI requiring urgent dialysis in 58% of the HIV-infected patients between 2002 and 2007. These findings are almost identical to a study by Williams reported in 1998. In contrast, the main causes of AKI in HIV patients in developed countries are predominantly nephrotoxicity, rhabdomyolysis, ischemia and dehydration (Izzedine et al, 2007). Other common causes include interstitial nephritis due to infections and drugs commonly used to treat or prevent opportunistic infections, as well as obstructive uropathy, crystalluria and other insults from the antiretroviral drugs.

## **2.2 Human Immunodeficiency virus (HIV) infection and the kidney**

The profound immunodeficiency from HIV infection is well described, and results primarily from the progressive deficiency of the subset of CD4-helper T cells. The CD4 receptor is vital for HIV entry, and the subsequent immune dysfunction, results in a high risk of developing opportunistic infections and neoplasms. The progression from infection to seroconversion, latent disease, early symptomatic infection and eventually advanced AIDS disease is well documented. Human Immunodeficiency Virus-associated nephropathy (HIVAN) is a common cause of end-stage renal failure, predominantly in black patients. Though timely interventions with antiretroviral (ARV) therapy and angiotensin converting enzyme inhibitors (ACEI) can reduce the progression of the disease, this aggressive glomerulopathy can advance to endstage kidney disease (ESKD) within weeks to months. It may be difficult to distinguish the effects of an acute insult to the kidneys from underlying HIVAN. The kidneys are typically normal or even increased in size even in advanced HIVAN, in contrast to the small kidneys found sonographically in most other forms of ESKD. To compound the issue, conditions frequently co-exist: in biopsies performed in a study on HIV-positive patients with presumed acute renal failure, 20% of the patients had HIVAN as the predominant underlying pathology (Arendse et al, 2011).

Given the complexity of HIV-associated renal failure and the impact of this increasing burden of disease on countries in sub-Saharan Africa, it would be important to be able to identify patients with potentially better outcomes from the severe case-load of critically ill HIV-positive patients, and apply limited resources in such a way that would offer the most benefit.

### 3. Objectives

With this literature review we planned to assess the survival of HIV-positive patients with AKI admitted to ICU, compared to the survival of those who were HIV-negative. If possible, we also wanted to identify factors which may predict poorer outcomes. The primary outcome to be assessed was survival in ICU, with our secondary outcomes being 30-day and 90-day post ICU survival, provided that sufficient data were available.

### 4. Methods

We searched the following databases: Pubmed (incorporating Medline), Web of Science (including Science Citation Index), Academic Search Premier, the Cochrane Library and Scopus (incorporating Embase) for all relevant literature up to June 2011. We used a controlled vocabulary of Medical Subject Headings terms, and free text, appropriately modified for the different databases. Included in the string sentence were the terms “acute renal failure” OR “ARF” AND “human immunodeficiency virus” OR “HIV” AND “Intensive Care Unit” OR “ICU”. The electronic search results yielded a total of 84 articles which were screened liberally from titles and abstracts and followed by the selection of full papers for inclusion in the review. Particular attention was paid to the possible inclusion of duplicate publications or overlap of databases in order to avoid the multiple inclusions of the same study.

All randomised control trials, case-control, and cohort studies investigating the survival of HIV-positive patients with acute renal failure compared to the survival of the general population with acute renal failure in ICU were to be included. Only studies published in the English language were included. In order to include the largest number of published articles, the definition of acute renal failure/acute injury was not limited to the RIFLE/AKIN criteria. We decided to distinguish clearly on mortality in ARV-naïve patients as compared to patients on ARV therapy if possible. Studies correcting for confounding factors were to be given preference.

### 5. Results

Our search yielded articles from 1988 to 2010. Of the 84 articles identified by our databases, 5 were identified by more than one database. One article was written in German and thus excluded, 5 were identified as posters, abstracts at congresses or personal correspondence and thus not available for scrutiny, and one article could not be accessed by the electronic resources from our library.

Seventy-two articles remained and were scrutinised carefully. Of these, 22 were dismissed as not being relevant to our review. Individual case studies numbered 8, all of which were discarded reducing the total of relevant articles to 42. Of these 3 dealt with HIV infection and respiratory illness; 1 reviewed the survival of HIV-positive paediatric patients in ICU without mentioning acute renal failure; 8 addressed HIV-positive patients in ICU due to respiratory failure or *Pneumocystis jiroveci* infection; 2 focused solely on acute respiratory failure without addressing HIV infection; 8 articles covered other systemic infections in patients with HIV without addressing ICU outcomes or AKI; 6 articles covered aspects of HIV infection with AKI but without assessing any Intensive Care aspect; 3 articles dealt with

AKI in the ICU but did not address any aspect of HIV infection, and 5 of the identified articles dealt with aspects of AKI only without addressing ICU or HIV infection.

Only 5 articles addressed all three of our key search items: HIV infection, intensive care and ARF/AKI. Of these, one listed the number of HIV-positive patients as 1% of their total study population without discussing outcome or comparison to the HIV-negative ICU patients with renal failure, and was thus discarded (Mehta et al, 2004). Another assessed the application of the RIFLE criteria for acute renal failure in critically ill HIV-infected patients, as well as their survival, but failed to compare it to the uninfected patients in their ICU, and was discarded as well (Lopes et al, 2007a). An article evaluating long-term risk of mortality after AKI in patients with sepsis was discarded because it only assessed the mortality of the group surviving ICU admission two years after their discharge (Lopes et al, 2010). The remaining two articles assessed the impact of acute renal failure on the HIV population in ICU retrospectively as single unit studies and identified it as a cause for increased mortality, but failed again to compare their outcomes with outcomes of patients from the general population with acute renal failure in ICU (Coquet et al, 2010; Lopes et al, 2007b).

## 6. Conclusion

There are insufficient publications available comparing the outcomes of HIV-positive patients with AKI admitted to ICU directly with that of the general population in ICU with acute renal failure in randomised control trials, cohort studies or retrospective studies to provide clear answers.

## 7. Discussion

Significant progress has been made in the treatment of HIV-disease since the early days of the pandemic, when the issues regarding acquired immunodeficiency syndrome patients and dialysis were still being debated (Pennel & Bourgoignie, 1988). It is commonly accepted that the outcome of patients with HIV is no different to other patients admitted to ICU (Rosen et al, 2006). Several publications have reported that critically ill patients with HIV infection have similar outcomes to other patients with a comparable severity of illness (Casalino et al, 1988; Forrest et al, 1988). Although outcome studies in patients with HIV infection are limited by retrospective analyses and subsequent selection bias a South African study (albeit with significant methodological limitations) confirmed this (Bhagwanjee et al, 1997).

In the ARV era, ICU survival of critically ill HIV-patients has increased significantly, despite unchanged disease severity (Coquet et al, 2010). Whereas ICU management of these patients was widely perceived as futile in the 1980s, mortality rates steadily declined as shown by a single-centre study, where co-morbidities and organ dysfunctions - but not HIV-variables were associated with mortality (Coquet et al, 2010). In this study, AKI was still independently associated with death, as it is in non HIV-infected ICU patients (Odds ratio 4.21; 95% Confidence interval). In a study on the long-term risk of mortality after AKI in patients with sepsis, HIV infection was not associated with increased 2-year mortality after discharge from the ICU (Lopes et al, 2010). This study, however, made no comparison between the in-ICU survival of HIV-infected patients who developed AKI associated with sepsis, and HIV non-infected patients.



Little prospective data are available on the survival of the subgroup of HIV-infected patients in ICU who develop AKI. A small single-centre study demonstrated a significantly higher mortality rate in ICU in HIV-infected patients who develop AKI compared to HIV-infected patients who do not. Sepsis was the most common associated aetiology (Lopes et al, 2007b). In a publication examining the same data, the authors assessed the RIFLE criteria for acute renal failure in these patients, and found that mortality increased significantly from normal to RIFLE class F (normal, 23.5%; class R, 50%; class I, 66.6% and class F, 72%;  $P < 0.0001$ ). The majority of their patients died within one month of ICU admission, but all survivors had complete recovery of renal function (Lopes et al, 2007a). When compared to a retrospective cohort study in seven intensive care units where the mortality rates for RIFLE class R was 8.8%, class I, 11.4% and class F 26% (Hoste et al, 2006), it would seem that HIV-infected patients have significantly worse outcomes. This comparison is however problematic, since neither differences in the severity of illness of the patients nor their subsequent renal management was corrected for.

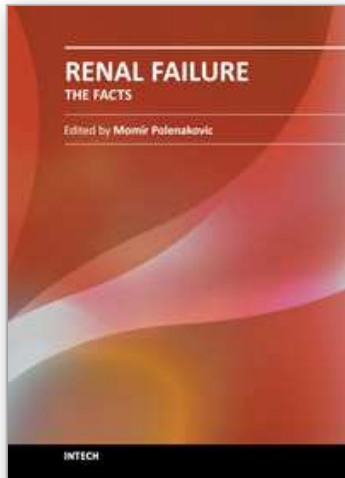
In conclusion, there are no prospective studies available comparing the outcomes of HIV-positive patients with AKI admitted to ICU directly with that of HIV uninfected ICU patients with comparable severities of illness. The available literature on patients with HIV infection in the ICU is most often confounded by single centre experience, reflecting local ICU admission criteria, and management, practice patterns and especially management of renal failure. Prospective studies are needed to provide further answers.

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Edited by Dr. Momir Polenakovic

ISBN 978-953-51-0630-2

Hard cover, 270 pages

**Publisher** InTech

**Published online** 23, May, 2012

**Published in print edition** May, 2012

The book "Renal Failure - The Facts" consists of some facts about diagnosis, etiopathogenesis and treatment of acute and chronic renal failure. Acute, as well as chronic renal failure is a great medical problem and their treatment is a burden for the budget of each government. The purpose of the chapters is to present some important issues of diagnosis and causes of AKI, as well as those caused by snakes and arthropods, after cardiac surgery, as well as some therapeutic achievements in AKI. Well presented are the psychological conditions in patients on haemodialysis, as well as the treatment of diabetic uremics. The book is aimed at clinicians with a special interest in nephrology, but it should also prove to be a valuable resource for any generalists who encounter nephrological problems in their day-to-day practice.

### **How to reference**

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J. D. Nel and M. R. Moosa (2012). The Outcome of HIV-Positive Patients Admitted to Intensive Care Units with Acute Kidney Injury, *Renal Failure - The Facts*, Dr. Momir Polenakovic (Ed.), ISBN: 978-953-51-0630-2, InTech, Available from: <http://www.intechopen.com/books/renal-failure-the-facts/the-outcomes-of-hiv-positive-patients-with-acute-kidney-injury-treated-in-intensive-care-units>

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