

Review Article**Infection and Renal Function****Rajeswari S¹, Swaminathan S²**¹Research Scholar, Department of Biochemistry, Vels University, Pallavaram Chennai- 600117, India.²Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai-60095, Tamilnadu, India***Corresponding author**

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Abstract: Kidney is generally prone to infections by all microorganisms and urinary tract infection is the first observed symptom. The first approach to identify is to calculate estimated glomerular filtration rate using serum creatinine to ascertain kidney function in any type of infection. HIV infection will lead to a host of renal impairment and renal markers to be evaluated after antiretroviral therapy. Established kidney failure patients are much more at a risk for infections particularly by HIV. Awareness about kidney disease manifestations and the complications are essential for treatment in all infections. This review articles highlights the research findings during the last two decades on kidney related disorders in infections by a variety of microorganisms notably HIV.**Keywords:** Kidney function, ART, HIV, Acute Renal Failure

INTRODUCTION

Kidney failure interferes with body's natural immunity making it easier to get some types of diseases like hepatitis or AIDS through dialysis treatment. The function of the kidney with its highly differentiated and specialized cell types is affected by infection with several viruses. Kidney disease is an important complication of HIV infection. Up to 30 percent of people living with HIV have abnormal kidney function, which can lead to end-stage renal disease (ESRD) leading to complete failure of the kidneys to work. The association between kidney function and infection-related hospitalization may be due to increased susceptibility to increased severity of infection which is predominant in older patients.

Infections by all types of Microorganisms are frequent in all confirmed cases of Acute Renal Failure (ARF), whether primary or secondary. The most frequent complications are septicemia, bacteremia, local complications and pulmonary or urinary tract infection (UTI). The most frequent infecting organisms are Staphylococcus (often methicillin-resistant) and gram-negative E. coli. Such frequent infections are serious as antibiotic therapy may lead to renal insufficiency stressing the importance of preventive treatment of prophylactic measures. Majority of death reported may be largely due to some of the persistent residual renal functional impairments [1]. The development of bacterial-induced renal failure in patients with cirrhosis and ascites is related to the Model for End Stage Liver Diseases (MELD) score

and to both the severity and lack of resolution of the infection. During infections, progressive form of renal failure that occurs in biliary are observed in all infections with ARF and gastrointestinal leading to spontaneous bacterial peritonitis (SBP) and UTI [2]. In such cases kidney biopsy revealed Antineutrophil Cytoplasmic Antibody (ANCA)-mediated focal Glomerulo Nephritis (GN) with 10% crescents and acute interstitial nephritis. Treatment with cyclophosphamide plus corticosteroids, but not with antibiotics alone resulted in resolution of both the ARF and the features of cerebral vasculitis. GN following bacterial infections may have various pathogenetic mechanisms presenting with complex diagnostic challenges and may be preventable in the case of hospital-acquired Methicillin Resistant Staphylococcus Aureus (MRSA) and may require immunosuppressive therapy in carefully selected and monitored cases [3].

In those with Chronic Kidney Disease (CKD) aggressive blood pressure control, use of Acetyl Choline Esterase (ACE) inhibitors, angiotensin receptor antagonists, blood glucose control in those with diabetes and avoidance of potentially nephrotoxic medications may slow the progression to ESRD. Awareness about kidney-disease manifestations and their implications are important to achieve success in confronting these ESRD problems [4]. Both postoperative ARF influence the frequency of serious infections after open-heart surgery and the infection rate was found to be higher in patients with postoperative ARF regardless of the baseline renal function (RF).

However, preoperative renal dysfunction portended higher risk of infection, independent of the influence of postoperative ARF [5]. Renal dysfunction was also found to be relatively uncommon among HIV-infected younger age group due to lack of comorbidities or as a result of not having proteinuria. Renal dysfunction was also found to be associated with duration of tenofovir (TDF) use. Factors associated with renal loss among TDF users included female gender, African American ethnicity and Cluster of Differentiation (CD4) nadir <200 cells/ μ L, and hence frequent monitoring of kidney function among these select HIV patients may be warranted [6]. Procalcitonin is a valuable marker of bacterial infections after major aortic surgery but RF is a major determinant of procalcitonin levels and thus different thresholds should be applied according to RF impairment [7].

Abacavir is a potent, novel 2'-deoxyguanosine analogue reverse transcriptase inhibitor (NRTI) which effectively suppresses HIV-1 replication, but to date there is no pharmacokinetic study in patients with renal impairment. Absorption, elimination and distribution phases were not altered by renal insufficiency and therefore, dosage adjustment is not necessary. In haemodialyzed patients, treatment could be administered independently during the dialysis session due to negligible elimination of abacavir in the dialysate [8]. TDF is associated with greater effect on decline in renal function and a higher risk of proximal tubular dysfunction in patients initiated with antiretroviral therapy (ART) [9]. Renal insufficiency is not uncommon, even in stable patients without diabetes or hypertension, but proteinuria was unexpectedly infrequent in this population. Utilizing resources to assess RF prior to initiation of ART in order to identify those likely to benefit from dosage adjustment is justified [10].

The Glomerular Filtration Rate (GFR) decreases after the first recognized UTI in childhood was well preserved. However, a significant reduction of individual GFR in the unilaterally scarred kidneys indicates that further follow-up is required, and even when bilateral scarring may happen, a more serious prognosis can be expected among them [11]. The prevalence of HCV antibodies was higher in patients with glomerulonephritis compared with patients diagnosed with interstitial nephritis, pyelonephritis, nephrosclerosis, diabetes mellitus, polycystic kidney and miscellaneous renal diseases. Higher prevalence of HCV antibodies in patients with GFR <30 mL/min compared with patients having > 30 mL/min suggesting that HCV infection may be associated with the pathogenesis of glomerulonephritis. Alternatively, glomerulonephritis or severe renal insufficiency may increase the likelihood of HCV infection [12]. The peak concentration of 3Thiacytidine (TC) increased with decreasing RF with increasing geometric means and terminal half life for patients with normal, moderate and

severe renal impairments respectively. The pharmacokinetics of 3TC is profoundly affected by impaired RF and hence dosage adjustment is warranted [13].

There is an urgent need for new biomarkers apart from eGFR that might help to identify tubular cell toxicity and predict the clinical outcome in HIV-infected patients. Increase in urinary beta-2-microglobulin and retinol-binding protein were observed in 70% of patients treated with TDF. Together with other tubular parameters or in isolation, both biomarkers could be useful for diagnosing proximal tubular toxicity. Other molecules, such as urinary kidney injury molecule-1, neutrophil gelatinase associated lipocalin, or N-acetyl- β -D-glucosaminidase could help to distinguish between tubular cell damage and dysfunction [14]. Renal insufficiency dramatically increases the risk of infection complicating pacemaker or implantable cardioverter defibrillator (ICD) surgery. This association should be part of the risk-benefit consideration prior to device implantation. Additional study of more extensive perioperative antibiotic therapy in this subset of patients is warranted [15]. Disorders in polymorphonuclear cell function are exacerbated by the dialysis procedure due to numerous factors including uremic toxins, iron overload, anemia of renal disease and dialyzer bioincompatibility. The phagocytic defect observed in ESRD is multifactorial and each factor should be managed individually with specific therapeutic approaches [16]. ARF is a cause of renal dysfunction in HIV-infected patients and its incidence and causes have not been studied since the introduction of Highly Active Antiretroviral Therapy (HAART) in HIV ambulatory patients. Immunosuppression, infection and HCV are important conditions associated with ARF in the post-HAART era [17].

A baseline eGFR should be calculated and RF should be monitored during ART. Renal transplantation has emerged as a feasible and successful modality of management of ESRD in HIV-infected individuals. Kidney Disease (KD) represents an increasing concern in the care of HIV-infected persons, although there are questions remains regarding the pathophysiology of HIV Associated Nephropathy (HIVAN). Transplantation, however, can be carried out safely in infected persons with ESRD [18]. Renal biopsy appears to be safe and useful for diagnosis and prognosis of the RF. High mortality rate is only observed in patients with ischaemic/toxic causes of ARF [19]. Polyomavirus infection causes nephropathy after kidney transplantation but has not been thoroughly investigated in nonrenal organ transplantation. BKV and JCV DNAs of polyomaviruses are commonly detected in the urine of lung transplant recipients; SV40 was found at low frequency. No definite impact of polyomavirus infection on RF was documented. BKV infection was associated with poor survival [20].

Chronic Kidney Disease (CKD) is significantly associated with major infectious complications and could be improved by using fewer dialysis catheters and increasing vaccination rates for influenza and pneumococcal pneumonia [21]. Clinicians must be aware that in cases of unexplained hepatitis in organ transplant recipients and in the absence of evident drug hepatotoxicity, HepatoEncephalus Virus (HEV) should be considered as an etiologic agent for hepatitis. Subsequently, HEV serological tests should be performed, HEV RNA should be looked for in acute-phase serum and stool samples and liver parameters should be monitored closely because HEV might be responsible in some cases for fulminant hepatitis [22]. Rosuvastatin 10 mg daily reduces plasma cystatin C and slows kidney function decline in HIV-infected patients on ART. Reductions in cystatin C with statin therapy correlate with reductions in inflammatory biomarkers. Relationships between cystatin C, kidney function, and cardiovascular risk in HIV may be mediated in part by inflammation [23]. Persistent RF abnormalities occur frequently in HIV-infected children. Improved survival, Black race and Hispanic ethnicity, and exposure to TDF, indinavir and other antimicrobial agents increase the risk for renal dysfunction. All HIV-infected children should be monitored closely for evidence of renal disease [24].

Disturbances in the renal microcirculation are responsible for ARF massive intravascular hemolysis leading to hemoglobinuria with or without renal failure; and immunologic reaction to parasites accounts for glomerular lesions. In addition, fluid and electrolyte disorders may result from the nonspecific effect of fever [25]. Both gram negative and positive microorganisms exhibited high degree of resistance to antimicrobial agents. Antibiotics like Gentamycin Sulphate, Polymyxin B and Colimycin Sulphate exhibited better range of total activity as compared to others [26]. Involvement of vital or large organs can contribute to morbidity and/or mortality in the affected patients. Major advances have occurred in the diagnosis and treatment of this disease with the potential for gene therapy or stem cell transplantation looming on the horizon [27].

KD related to the direct effects of HIV may be prevented by ART and it remains an important issue in HIV-infected individuals leading to a high prevalence of other risk factors, such as hepatitis C, cigarette smoking and injectable drug use. Only with greater awareness on KD manifestations in HIV patients and their implications particularly in vulnerable population, we will be able to achieve success in confronting this growing problem [28]. Renal impairment was common, though rarely severe, among HIV-infected adults with clinically non-advanced HIV disease. Renal dysfunction has been demonstrated to be a risk factor for early mortality and they are relevant for ART programmes,

such as those in Malawi where RF is not routinely assessed [29]. High incidence of TDF associated RF decline among patients with low Body Mass Index (BMI). Additional risk factors are baseline GFR in those receiving protease inhibitor and nephrotoxic drugs. Close monitoring of RF is warranted among patients with these risk factors [30].

Early identification through efficient screening and prompt treatment of KD in HIV-infected individuals are critical for better outcome. Clinical and epidemiological issues and treatment strategies such as dialysis and kidney transplantation should be closely monitored in HIV population [31]. Strategies to prevent or retard progression to ESRD of HIV-associated kidney conditions should include urinalysis and measurement of kidney function tests in all people with HIV at presentation. Renal replacement in the form of dialysis and transplantation should be implemented as appropriate [32]. Several ARVs are associated with chronic renal impairment, but the extent of such adverse events among HIV positive persons with initially normal RF is unknown. TDF, ritonavir-boosted atazanavir and lopinavir uses are independent predictors of chronic renal impairment in HIV-positive persons without preexisting renal impairment. Increased TDF discontinuation rates with decreasing eGFR may prevent further deteriorations. After discontinuation, the ARV-associated incidence rates decreased [33]. TDF-associated renal impairment is not uncommon in a real-life practice due to potentially irreversible adverse effect of this agent, particularly in patients with vulnerable kidneys and concomitant use of both TDF and boosted Protease inhibitor [34]. KD represents an increasing concern in the care of HIV-infected persons, although there are questions remaining regarding the pathophysiology of HIVAN. Transplantation, however, can be carried out safely in infected persons with ESRD [35]. The effect of TDF on RF has been measured in multiple studies. Although African Americans are at a higher risk of developing CKD only limited data are available on the influence of race on TDF-related nephrotoxicity. Elevated baseline serum creatinine and female gender may be potential predictors for TDF discontinuation. No statistically significant differences in TDF-related RF changes by race was observed in HIV patient population [36]. Significant associations were found between leucocytes and non-steroidal anti-inflammatory drug (NSAID) use, previous history of tuberculosis, low BMI, female gender and between PRO and high viral load. CKD evaluation suggests a potentially high prevalence of it among people living with HIV (PLWH) in Burundi. Patients should be regularly monitored and preventative measures, such as monitoring the use of Non Steroidal Anti-inflammatory Drugs and adjustment of drug dosages according to body weight should be implemented. Urine dipsticks could be used as a screening tool to detect patients at risk of renal impairment [37]. Despite the beneficial effect of ART in preventing and treating HIVAN and

possibly other forms of KD in persons living with HIV, some of these medications, including TDF, indinavir and atazanavir can induce acute and/or chronic kidney injury via mitochondrial toxicity or intratubular crystallization. Further research is needed to better understand factors that contribute to acute and chronic kidney injury in HIV-positive patients and to develop more effective strategies to prevent and treat KD in this vulnerable population [38].

Studies have shown a high prevalence of renal impairment in HIV positive individuals with higher rates among highly active ART naïve individuals. It also indicates the importance of assessing RF in HIV positive individuals in general and in highly active ART naïve and with low CD4 count in particular. Further cohort studies with larger sample size are also important to establish the prevalence rate of renal impairment [39]. TDF is a potent nucleotide analogue reverse-transcriptase inhibitor used with other antiretroviral agents for the treatment of HIV infection. Despite the absence of renal toxicity observed in the major clinical trials of TDF, several case reports of ARF and proximal tubule dysfunction have been described [40]. Data on the renal safety of TDF in Low and Middle Income Countries are scarce. There is higher frequency of treatment limiting renal impairment events amongst PLWHA receiving TDF in Western India. As TDF scale up progresses, programs need to develop capacity for monitoring and treatment of renal impairment associated with TDF [41]. The risk of renal disease was also found to increase significantly with age. PLWHA are at increased risk of renal disease, with greater risk at later stages of infection and at older ages. ART prolongs survival and decreases the risk of renal disease. However, less reduction in renal disease risk occurs for TDF-containing ART than for other regimens [42]. There was no significant correlation between proteinuria and the duration of infection from the time of diagnosis. Albuminuria also demonstrated a significant negative correlation with the levels of haemoglobin and low CD4 cells were associated with lower levels of haemoglobin [43].

Penicillin therapy alone could resolve proteinuria in renal failure. This response strongly suggest that there is a causal relationship between syphilis and nephrotic syndrome [44]. Although syphilis has been associated with membranous glomerulopathy and post-infectious glomerulonephritis, a latent syphilis with rapidly progressive glomerulonephritis has been identified. The presence of treponemal antigen and antitreponemal antibody in glomeruli supports the association of these two entities [45]. Syphilis is called 'the great imitator' and keeps surprising us time after time since better treatment options for HIV are available making this a chronic instead of fatal infection as safe sex is practised less. As a consequence, the incidence of syphilis is rising rapidly now. Therefore, we can expect rare and unlikely

manifestations of syphilis to occur more often in the near future [46]. In hospitalized AIDS patients, hypomagnesemia is a risk factor for non recovery of RF and for in-hospital mortality. Further it is important to determine whether hypomagnesemia is a determinant or simply a marker of critical illness and studies involving magnesium supplementation in AIDS patients are warranted [47]. Patients with AIDS and Toxoplasma encephalitis may have several predisposing conditions that can lead to the development of sulfadiazine-induced crystalluria, including poor fluid intake, fever, diarrhea, and hypoalbuminemia, in addition to the high doses of the drug required and the prolonged period of treatment. This potentially serious complication can be managed easily with conservative treatment. Clinicians should be aware of this complication as it is expected to occur more frequently as more patients are treated with sulfonamides and patients with AIDS experience longer survival rates [48]. Early identification through efficient screening and prompt treatment of KD in HIV-infected individuals are critical to lead to better outcomes [49]. Dosage adjustments are not necessary for creatinine clearances of greater than 35 mL/min, as multiple dosing leads to increased trough concentrations and drug accumulation, lower dose regimens may still be efficacious, yet associated with reduced toxicity [50].

In HIV-seronegative men who have sex with men, randomization to TDF with emtricitabine was associated with a very mild nonprogressive decrease in GFR that was reversible and managed with routine serum creatinine monitoring [51]. TDF disoproxilfumarate, a prodrug of TDF, is a potent nucleotide analogue reverse-transcriptase inhibitor with activity against HIV. Although initially thought to be relatively safe with regards to nephrotoxic effects compared to its class drugs-adefovir and cidofovir, several cases of ARF and proximal tubule dysfunction have been described in the last few months. Fanconi syndrome may interfere with TDF treatment as discontinuation this drug has improved a patient's condition [52].

Screening for proteinuria and albuminuria allows identification of patients at higher risk of KD and other adverse outcomes. Fanconi syndrome, which has been associated with TDF use, is associated with severe tubular proteinuria, and several low molecular weight proteins, including retinol-binding protein, β -microglobulin, and neutrophil gelatinase-associated lipocalin have been studied as markers of tubular dysfunction. Studies have reported a high prevalence of subclinical proximal tubular dysfunction in patients receiving ART [53]. HIV-infected patients may develop a variety of structural lesions in addition to Focal Segmented Glomerulosclerosis (FSGS), and show that FSGS, when it occurs, is not uniformly accompanied by rapid progression to ESRD. The reasons for this difference from experience reported by other centers may relate to a lower proportion of blacks and of

patients with intravenous drug abuse as an AIDS risk factor seen at Focal Segmentary Glomerular Hyalinosis (SFGH) [54]. Reduced RF is associated with progression to AIDS but not with overall mortality in HIV-infected kenyan adults not initially requiring combination of ARI [55]. RF measurement in resource-limited settings may be an inexpensive method to identify those most in need of cART to prevent progression to AIDS. The initial association between reduced GFR, but not reduced eGFR, and greater mortality was explained by the low weights in this population [56]. Renal biopsy is indicated in renal dysfunction associated with HIV for making proper diagnosis and therapy [57].

CONCLUSION

This review article has highlighted the various research findings during the last two decades on infection related kidney disorders both in normal as well as existing kidney failure patients. Infections by HIV and syphilis and the various Antiretroviral therapies are also highlighted. Kidney diseases represents an increasing concern in case of HIV infected person and prompt treatment are critical for better outcomes. The effect of antimicrobial agents like Tenofavir, penicillin therapy increases the risk of renal dysfunction. This review article content will give awareness among researchers to further explore research in this field of infectious diseases that causes renal dysfunction, appropriate treatment and prognostic outcome in such patients.

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