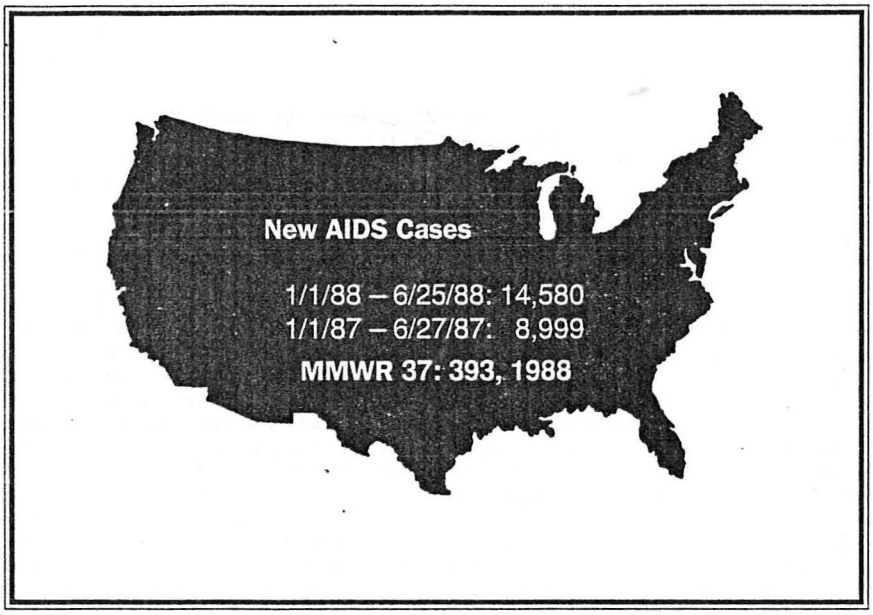
RENAL AND ELECTROLYTE DISORDERS IN PATIENTS WITH AIDS



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INTRODUCTION

It is well recognized that the acquired immunodeficiency syndrome (AIDS) is frequently associated with dysfunction of the immune, hematopoietic, respiratory, gastrointestinal and central nervous systems. Recently, several centers have reported that renal disorders also occur with substantial frequency in patients with AIDS. It is the purpose of this review to examine the types of renal and electrolyte disorders occurring in patients with AIDS and related illnesses due to infection by the human immunodeficiency virus (HIV).

HISTORICAL PERSPECTIVE

Cases of AIDS first appeared in the United States in the late 1970's; the existence of this syndrome was first recognized in the early 1980's (Hardy, 1987). In 1982, the case of a patient with AIDS, nephrotic syndrome, cryoglobulinemia and hepatitis B was reported (Case Records of the Massachusetts Hospital, 1982). Renal biopsy showed a proliferative glomerulonephritis and evidence of immune complex accumulation along glomerular capillary loops and in the mesangium. Further studies suggested that hepatitis B surface and e antigens were present within glomeruli. Since hepatitis B can be associated with nephrotic syndrome and glomerulonephritis, it is likely that this patient's renal disease was more closely related to hepatitis than to AIDS. Autopsy series primarily concerned with the systemic manifestations of AIDS began appearing shortly after this publication. In 1983, Reichert and colleagues reported the autopsy pathology of 10 AIDS patients referred to the National Institutes of Health in Bethesda. They found glomerular inclusions consistent with CMV infection in two patients and noted that one of these patients had severe azotemia. However, the remainder of the patients in this series did not appear to have clinicopathologic evidence of renal disease or dysfunction. Subsequent autopsy series also found only infrequent evidence of renal disease in AIDS patients (Guarda, Houston, 1984; Hui, Los Angeles, 1984; Welch, San Francisco, 1984; Niedt, New York City, 1985), and although occasional patients were found to have had opportunistic infections or Kaposi's sarcoma within the kidney, it was not clear that such renal involvement commonly achieved clinical significance.

In 1984, roughly simultaneous publications of clinical series by Rao et al and Gardenswartz et al suggested that a substantial number of the AIDS patients treated at specific New York City hospitals had heavy proteinuria, azotemia or both (Rao, 1984; Gardenswartz, 1984). Rao and colleagues found that 12% of their patients excreted more than 3.5 g of urinary protein per 24 hours or had azotemia with lesser amounts of proteinuria. Most of these patients had focal and segmental glomerulosclerosis (FSGS). Gardenswartz et al found that 41% of AIDS patients in a retrospective review had abnormal levels of proteinuria, renal insufficiency or both. Both groups found that AIDS patients developing renal disease deteriorated rapidly and had a substantially poorer prognosis than AIDS patients without renal disease.

Later in 1984, Pardo et al reported that 43% of prospectively studied AIDS patients treated at the University of Miami excreted more than 0.5 g of urinary protein per 24 hr; 9% excreted more than 3 g per 24 hr; and 47% of the patients undergoing autopsy had glomerular changes ranging from mild mesangial

proliferation to FSGS (Pardo, 1984). They noted that heavy proteinuria correlated with the presence of FSGS. They also observed that acute renal failure occurred frequently in their AIDS population and sometimes presaged a rapid demise, although some instances were reversible. The series of Rao and Pardo have been updated recently and will be reviewed in detail later in this review.

Taken together, the series of Rao, Gardenswartz and Pardo suggest that renal disease, particularly renal disease manifest by heavy proteinuria, is prevalent in AIDS patients living in certain urban areas of the United States. Additional series and anecdotal reports from New York City, Cincinnati, Los Angeles and Detroit support the same conclusion (Weiss, 1986; Chander, 1987; D'Agati 1987a, 1987b; Kaplan, 1987; Provenzano, 1987; Cohen, 1988a; Langs, 1988). In addition, Vaziri and colleagues from Irvine, California find a high incidence of clinically significant acute renal failure in their series of AIDS patients. On the other hand, groups in Bethesda (Balow, 1986) and San Francisco (Humphreys, 1987; Mazbar, 1988) find little clinical or histological evidence that glomerular disease is prevalent in their respective areas. It is especially notable that Humphreys et al observe only infrequent heavy proteinuria and azotemia in the large population of AIDS patients in San Francisco. Thus, there is disagreement as to the frequency of renal disease in AIDS patients. The work of D'Agati and colleagues is relevant in this regard (D'Agati, 1987b). They reviewed antemortem renal biopsies of 37 AIDS patients and the postmortem renal histology of 30 additional AIDS patients from New York City. Most of the patients selected for biopsy had FSGS, but only one of the patients included in the autopsy series had FSGS. It is evident, therefore, that the process of patient selection can have a major impact on estimates of disease frequency. However, the prospective series of Rao and Pardo (see below) continue to indicate that clinically significant proteinuria and renal insufficiency occur with substantial frequency in New York and Miami. It seems likely, therefore, that clinically significant renal disease occurs frequently in some areas but not in others at this time.

RENAL DISEASE IN AIDS PATIENTS AUTOPSIED AT SOUTHWESTERN

The above controversy prompted us to review the records and autopsy material from the first 50 AIDS patients autopsied at the University of Texas Southwestern Medical Center (Seney, Burns, Silva, and Baker). The patients in this series constitute approximately 20% of AIDS cases diagnosed at Parkland Memorial Hospital and the Dallas VA Medical Center between December, 1983 and August, 1987. All patients fulfilled currently accepted criteria for the diagnosis of AIDS (CDC, 1988). The demography of these patients is reviewed in Table 1.

Table 1
Characteristics of 50 Consecutive AIDS Patients Autopsied at Southwestern Medical Center

Male	96%
Female	4%
Age at death, avg.	35
Risk factors for AIDS	
IV drug use	32%
Homosexuality or bisexuality	74%
Other or unkown	14%

We are determining the frequency of clinically apparent renal and electrolyte disturbances by retrospective review of charts. Preliminary results for selected diagnoses are listed in Table 2.

Table 2
Frequency of Selected Diagnoses in 50 AIDS Patients Autopsied at Southwestern Medical Center

Renal Failure	12%
Proteinuria	10%
Renal enlargement	0%
Hyponatremia	30%
Hyperkalemia	20%
Hypocalcemia	30%

Instances of clinically apparent renal failure were usually either transient and attributable to nephrotoxic drugs or occurred in the preterminal state when respiratory dysfunction and hypotension were common. Proteinuria was usually minimal or undetectable by urinalysis and, when quantitated by 24 hr urinary collection, was usually within or near the normal range. However, a substantial fraction of our patients had hyponatremia, hyperkalemia or both. In most instances, these disturbances were transient. In others, hyponatremia and/or hyperkalemia occurred in the phase of the patient's illness immediately before death. Hyponatremia often occurred in conjunction with GI fluid loss, but also occurred in conjunction with pulmonary and CNS disease such that the syndrome of inappropriate ADH release was considered. Testing of adrenal function was performed in some instances either by measuring random cortisol levels or by measuring cortisol levels before and after administration of ACTH. None of these patients was found to have overtly deficient glucocorticoid production at the time of testing. Hypocalcemia was common, partly on the basis of hypoalbuminemia. Several patients, however, had degrees of hypocalcemia out of proportion to the degree of hypoalbuminemia. In spite of this, clinical signs of hypocalcemia were usally not evident.

In the same series of 50 patients, formalin-fixed renal tissue was prepared for and examined by light microscopy. Findings are shown in Tables 3 and 4:

Table 3
Glomerular Findings in 50 AIDS Patients Autopsied at Southwestern Medical Center

Global sclerosis (~ 10% of glomeruli)	8%
Focal and segmental glomerulosclerosis (FSGS)	8%
Focal and segmental mesangial hypercellularity	8%
Enlarged glomeruli	6%
Glomerular thrombosis	4%
Multinucleated visceral epithelial cells	4%
Ischemic changes	2%
Glomerular destruction by cryptococci	6%

Table 4
Extraglomerular Findings in 50 AIDS Patients Autopsied
at Southwestern Medical Center

Renal tubular casts	66%
Nephrocalcinosis, cortical	38%
Nephrocalcinosis, medullary	36%
Nephrocalcinosis, cortical and medullary	30%
Focal interstitial nephritis	38%
Tubulointerstitial involvement by:	
CMV, definite inclusions	12%
CMV, suspected	28%
Cryptococci	6%
Histoplasmosis	4%
Mycobacterium avium intracellulare	4%
Granuloma or microabscess, organism not determined	4%
Hyaline droplets in early proximal tubule	12%
Thinned proximal tubule epithelium	26%
Acute tubular necrosis	8%
Lymphoma	4%

The most striking observations of this study pertain to the high frequency of tubular and interstitial findings in the kidney. Among these findings, the high frequency of interstitial nephritis is consistent with published reports and is not surprising for at least two reasons. First, as shown above, opportunistic microorganisms frequently invade the tubulointerstitial region of the kidney. In response to such infections, it is clear that many AIDS patients can still develop an inflammatory response even in the face of profound immunosuppression. Second, many drugs with the potential to cause allergic interstitial nephritis are given to AIDS patients. Such drugs include penicillins and trimethoprim/sulfamethoxazole, which are known to cause allergic interstitial nephritis with some frequency in the general population.

The high incidence of nephrocalcinosis was unexpected. A few patients with nephrocalcinosis have been previously reported (Gardenswartz, 1984; Falkoff, 1984; Niedt, 1985; Chander, 1987; D'Agati, 1987b), but some of these had received amphotericin B, which is well known to cause nephrocalcinosis. Most of our patients with nephrocalcinosis had not received this drug. It is not clear why they developed nephrocalcinosis, but it is noteworthy that our patients with nephrocalcinosis were more likely to develop hypocalcemia than patients without nephrocalcinosis.

In contrast to extraglomerular findings, major glomerular findings were not common in our study. Moreover, significant glomerular dysfunction was also uncommon. It should be noted, however, that 12% of our patients had hyaline droplets in the early proximal tubule. Such droplets usually appear when defective glomerular permselectivity permits abnormal amounts of plasma proteins to enter tubular fluid. Thus, despite the paucity of clinically evident glomerular disease in our series, subclinical glomerular disease appears to have occurred in several instances. It should also be noted that 8 individuals with AIDS or evidence of HIV infection without AIDS have been

treated for heavy proteinuria and/or renal failure in this institution over the last 18 months. None of these patients became part of our autopsy series. Three of these patients underwent percutaneous renal biopsy (Dr. Jeff Thompson, personal communication, July, 1988). Two with heavy proteinuria had FSGS. The third had azotemia and hematuria without heavy proteinuria. He had interstitial fibrosis without significant glomerular lesions. Therefore, although clinically significant glomerular disease does not appear to occur in AIDS patients from the Dallas metropolitan area with the same frequency observed in New York and Miami, it is certainly not a rare problem.

"AIDS/HIV-ASSOCIATED NEPHROPATHY"

A broad variety of renal lesions have now been observed in patients with AIDS. These range from the interstitial lesions described above to glomerular lesions including FSGS, acute postinfectious glomerulonephritis, membranoproliferative glomerulonephritis, minimal change disease, amyloidosis and hemolytic uremic syndrome (references previously cited; Boccia, 1984; Singer, 1985; Guerra, 1987; Kim, 1987; D'Agati, 1987a, 1987b; Rousseau, 1988, Mazbar, 1988). Such variety brings into question whether there is any cause and effect relationship between AIDS and renal disease. However, the recently updated reports of Rao et al and Pardo et al suggest that AIDS patients can develop a clinical syndrome characterized by nephrotic syndrome and varying degrees of renal failure (Rao, 1987; Pardo, 1987; Bourgoignie, 1988). These and related reports will be reviewed in this section.

In 1987, Rao et al reviewed their series of AIDS patients included in a prospective registry of patients treated at the State University of New York, Health Science Center at Brooklyn between January, 1982 and December, 1986 (Rao, 1987). In this period, they identified a total of 750 AIDS patients, a group constituting 8% of AIDS cases diagnosed throughout New York City and 46% of cases reported in Brooklyn during the same period. Among these patients, 6% of whom were white, nearly half were intravenous drug addicts, 20% were homosexual men and 28% were Haitian immigrants to the United States. Members of the Renal Service at SUNY Brooklyn evaluated 78 (10.4%) of these patients. They also identified an additional 18 patients who developed AIDS after initiation of hemodialysis for end stage renal disease initially attributed to intravenous drug addiction. This provided a total of 96 patients, who were classified in 3 groups. Group I patients initially had no evidence of renal disease but developed acute renal failure attributed to nephrotoxins, dehydration, sepsis, shock or respiratory insufficiency. Group II patients developed "AIDS-associated nephropathy" defined as nephrotic syndrome or progressive renal failure leading to irreversible uremia over 4 to 16 weeks in the absence of nephrotoxins or ischemic factors. Group III comprised the 18 patients who developed AIDS while on dialysis. Characteristics of Groups I through III are shown in Table 5.

Table 5
Renal Disease in AIDS Patients, Brooklyn
Rao et al (N Engl J Med 316:1062, 1987)

		Peak Serum Creatinine (mg/dl)	
	n	2-6	>6
Group I	23	6	17
Group II	55	12	43
Group III	18	0	18
Total	96	18	78

It follows from this table that 1 out of every 10 AIDS patients seen at SUNY Brooklyn developed clinically signficant renal failure. Group I patients represented 3.1% of the 750 patients in the AIDS registry at SUNY Brooklyn. The majority of patients with acute renal failure and severe azotemia were not dialyzed because of hemodynamic instability or decision by the physician and family. Such patients died within 3 weeks, although renal function had improved by the time of death in 3 instances. Six patients in group I did undergo dialysis, and 5 experienced return of renal function such that dialysis was no longer necessary. Four of these patients survived for periods of 10 to 24 months. Group II, the largest of the three groups, represented 7.3% of the patients in the registry. All of the patients in this group were black, 89% were male, 55% used intravenous drugs and 25% had recently entered the United States from Haiti. Only 9% were homosexual. At the time of presentation, most of these patients had the nephrotic syndrome with or without renal failure. Renal histologic examination demonstrated FSGS in 90% of the patients from whom tissue was obtained. The remainder had mesangial changes. Nearly half of the patients in Group II developed end stage renal disease within 4 to 16 weeks after the onset of proteinuria or azotemia (an unusually rapid pace compared to previously described forms of FSGS). The majority (78%) of Group II patients ultimately developed end stage renal disease. Some of these patients were not dialyzed for a variety of reasons. However, 31 of 43 patients with end stage renal disease did receive dialysis. The clinical course of these patients was complicated by severe cachexia, which developed despite intensive efforts to augment caloric intake. Death due to malnutrition or intercurrent infection nearly always ensued within 6 months. Only two patients were able to leave the hospital after the development of end stage renal disease.

The characteristics of patients in Group III were similar to those of Groups II except that evidence of AIDS was lacking when end stage renal disease was first diagnosed. All Group III were black, had the nephrotic syndrome and had histories of IV drug addiction, which was initially presumed to be the cause of their renal disorders. However, after a mean period of 16.2 months (range 2 to 64 months), the patients in this group developed symptoms suggestive of AIDS. Ultimately, all developed opportunistic infections and rapidly succumbed of intercurrent infection or cachexia as shown in Table 6.

Table 6:

Characteristics of 18 Patients with AIDS Diagnosed During Maintenance Dialsis. Rao et al (New Engl J Med 316:1062, 1987).

Age/Sex	Start of Dialysis	Diagnosis of AIDS	Date of Death	Survival after Diagnosis
		date		*mo*
35/M	3/82	9/82	11/82	2
31/M	11/83	4/84	5/84	1
24/M	9/83	4/84	5/84	1
35/M	2/84	8/84	10/84	2
30/M	5/84	10/84	10/84	<1
27/F	6/85	8/85	9/85	1
32/M	1/85	9/85	10/85	1
26/M	10/84	8/85	9/85	1
36/M	4/82	8/85	10/85	2
44/M	9/84	1/86	2/86	1
50/M	4/85	8/85	9/85	1
42/M	11/85	2/86	3/86	1
35/M	1/80	4/86	6/86	2
30/M	3/83	6/86	7/86	2
31/F	2/85	4/86	7/86	3
35/M	7/86	10/86	12/86	2
33/M	3/86	10/86	12/86	2
33/M	6/82	11/86	12/86	2

Thus, patients in Group III had a prognosis as bad as that of patients in Group II. Furthermore, like Group II patients, nearly all Group III patients from whom renal tissue was obtained had FSGS. Since publication of this report, Rao et al have seen still more patients like this (Rao, 1988). They now believe that nephrotic syndrome and azotemia in IV drug users can be the initial clinical manifestations of AIDS.

Bourgoignie, Pardo and colleagues have also recently updated the results of their prospective studies of patients with AIDS or AIDS-related complex (ARC) admitted to the University of Miami-Jackson Memorial Medical Center between January, 1982 and June, 1986, when 1,263 patients with AIDS/ARC were seen at this institution (Bourgoignie, 1988). The Nephrology Service evaluated 6.3% of these patients, mainly for proteinuria and azotemia but occasionally for hyponatremia as well. Among these patients, a substantial number had progressive renal insufficiency, as reflected by their serum creatinine values shown in Figure 1.

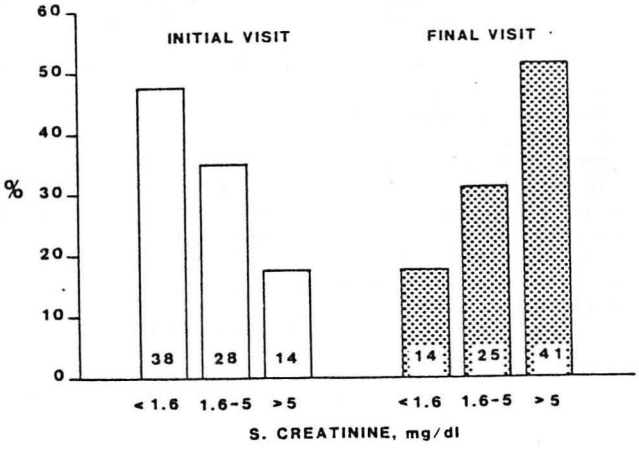


Figure 1:

Progressive Renal Failure in 80 Patients with AIDS or ARC, Miami. Bourgoignie et al (Adv Nephrol 17:113, 1988). N = 80 patients. The figure at the base of each bar is the number of patients for that particular group.

They also found a number of instances of acute renal failure, some of which were reversible. However, end stage renal disease was common among patients with nephrotic syndrome and usually indicated imminent death despite dialysis.

In addition, Pardo et al recently reported the results of detailed histologic studies on renal tissue obtained from 159 patients with AIDS or AIDS-related complex (Pardo, 1987). Tissue was obtained from 24 patients selected for renal biopsy. Tissue from the remaining patients was obtained from 135 consecutive autopsies. In this series, Pardo and colleagues found that 32% of 131 adults had abnormal glomerular histology. Three quarters of these patients had FSGS, which was usually accompanied by the syndrome of renal enlargement, heavy proteinuria (mean 7.2 g per day) and/or renal insufficiency (mean serum creatinine 5.4 mg/100 ml). Patients in this subgroup were predominantly black (39% were of Haitian extraction) and were more likely

to have a history of intravenous drug addiction than homosexual or bisexual behavior. The remaining quarter of adults with glomerular disease had either focal or diffuse mesangial hyperplasia. This subgroup tended to differ from the patients with FSGS several ways. First, nearly half were white. Second, nearly half were known to be homosexual; only 9% were known to use intravenous drugs. Third, these patients did not have clinically imporant renal disease or enlargement. Patients with FSGS often developed uremia and rapidly died despite dialysis.

In the same study, 28 children were studied. All were black, 68% were of Haitian extraction. Fourteen percent, ranging in age from 2 to 5 years, developed FSGS manifest clinically as nephrotic syndrome. Another 14%, ranging in age from 7 months to 3 years, had mesangial hyperplasia without clinical evidence of renal disease. Renal disease did not adversely affect survival in these children (Pardo, personal communication, July, 1988).

Thus, on the basis of studies by Rao and Pardo, it seems that the association of FSGS and AIDS is observed more commonly than can be explained by fortuity alone. Furthermore, it appears that adults with AIDS or ARC in New York and Miami are at increased risk for the development of a particular syndrome characterized by nephrotic levels of proteinuria, FSGS and rapidly progressive renal failure. This syndrome has been termed AIDS-associated nephropathy or HIV-associated nephropathy. Other groups in New York City (Gardenswartz, 1984; Chander, 1987; D'Agati, 1987; Kaplan, 1987; Langs, 1988) as well as groups in Cincinnati (Weiss, 1986), Detroit (Provenzano, 1987), Los Angeles (Cohen, 1988a), Montreal (Rousseau, 1988) and Paris (Dosquet, 1988) have observed patients with similar syndromes. On the basis of these studies, therefore, it is tempting to conclude that HIV-associated nephropathy is a real and widespread entity. However, if it does exist, two caveats must be kept in mind. First, HIV-associated nephropathy is currently not observed with detectable frequency in all areas (e.g., Bethesda, San Francisco and Dallas). Second, patients with AIDS or ARC can also develop acute renal failure and a variety of glomerular lesions other than FSGS.

IS THERE A VARIANT OF FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS SPECIFIC FOR AIDS?

Although there is considerable evidence that FSGS occurs frequently in certain parts of this country and perhaps in other countries as well, it is problematic to argue that AIDS and FSGS are necessarily causally related. FSGS is a nonspecific histopathologic characterization rather than a specific clinicopathologic entity. It has been reported to occur in conjunction with intravenous drug use, vesicoureteral reflux, unilateral renal agenesis, obesity and a variety of other conditions in addition to AIDS (Silva, 1988). There is also an idiopathic variety. However, three lines of evidence suggest that a peculiar variant of FSGS occurs in patients with AIDS. First, the patients with AIDS who develop FSGS seem to have a fulminant lesion that often leads to end stage renal failure over a period of 4 to 16 weeks (see above). In contrast, the variety of FSGS associated with IV drug addiction usually progresses to end stage over months to years; the idiopathic forms of FSGS often require several years to reach end stage. Second, FSGS in AIDS patients has unusual light microscopic features shown in Table 7.

Table 7: Unusual Light Microscopic Features of FSGS in AIDS Patients*

1. Glomerulosclerosis more global and diffuse than in idiopathic FSGS. (Hence, there may be a better term than "focal and segmental" GS).
2. Severe retraction of glomerular capillaries.
3. Little or no increase in mesangial matrix. Minimal amounts of glomerular hyalinosis.
4. Prominent visceral epithelial cell hypertrophy with increased size and number of intracytoplasmic vacuoles/droplets.
5. Association with prominent tubulointerstitial changes including tubular degeneration, dilation and cast formation.

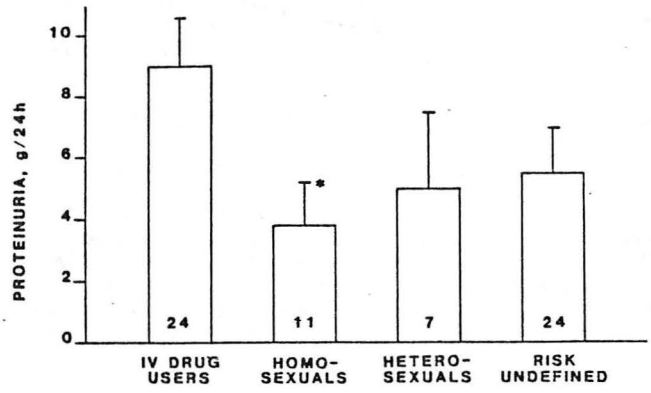
* (D'Agati, 1987b; Chander, 1987; Cohen, 1988a; Pardo, 1988)

Cohen and Nast, Chander et al and Pardo et al emphasize that prominent interstitial edema, tubular degeneration, proteinaceous tubular casts and tubular dilation occur with considerable frequency in AIDS patients with FSGS, unlike HIV-negative patients with IV drug nephropathy or AIDS patients with immune complex glomerulonephritis (Cohen, 1988a; Chander, 1987; Pardo, 1988). Third, electron microscopy by Chander and others demonstrates the presence of "tubuloreticular structures" (TRS) in the vascular endothelium of kidneys from AIDS patients with FSGS (Chander, 1987; Cohen, 1988a; Pardo, 1988). TRS can be seen in a number of tissues in conjunction with various disease entities. For example, they appear as the "myxovirus-like" particles in patients with lupus erythematosus. They have also been seen in cultured cells exposed to alpha interferon. Thus, they cannot be regarded as specific for AIDS patients, (though perturbations of alpha interferon levels may be common in AIDS patients). TRS are readily demonstrable in extrarenal tissues of AIDS patients (Sidhu, 1985) and in renal endothelial cells of AIDS patients with FSGS (Chander, 1987; Cohen, 1988a; Pardo, 1988). However, Chander et al and Cohen and Nast find no evidence of such structures in the kidneys of patients with IV drug-related FSGS or in AIDS patients with immune complex glomerulonephritis. They suggest, therefore, that these lesions, when present in the kidneys of patients with AIDS/FSGS, serve as markers of a unique entity related to AIDS. Recently, Cohen and colleagues have been able to demonstrate presumptive evidence of direct HIV infection of renal tissue in AIDS patients with FSGS (Cohen, 1988b). Using a cDNA probe directed against HIV nucleic acid, they found evidence of viral invasion of proximal tubular cells and glomerular epithelium in 10 of 10 cases. It remains to be shown whether this finding is specific for AIDS patients with FSGS. Pending further studies, however, this finding together with the information reviewed above is consistent with the hypothesis that AIDS patients can develop a specific form of FSGS.

If this hypothesis is correct, it must be explained why investigators in different parts of the country have such different experiences with respect to renal disease in AIDS patients. This may be due in part to considerable differences in patient populations. The series based in New York and Miami primarily involve blacks. The series based in San Francisco and Bethesda primarily involve whites. It appears that black patients are more prone to develop FSGS in conjunction with intravenous drug use than other racial groups

(Friedman, 1983). Perhaps racial factors also predispose the development of FSGS in black patients with AIDS. However, this explanation is not sufficient to account for all cases since FSGS clearly occurs in nonblack patients with AIDS. The series from New York and Miami also involve large numbers of IV drug addicts, unlike the populations treated in San Francisco and Bethesda. As mentioned earlier, IV drug addiction may be an independent risk factor for the development of FSGS. It is germane, therefore, that Bourgoignie et al find a positive correlation between IV drug use and the level of proteinuria in their patients with AIDS or ARC as shown in Figure 2.

Figure 2
Levels of Proteinuria in AIDS/ARC Patients,
Correlation with Risk Factors



Average level ± 1 SEM, (g/24 hr). *p = 0.05 vs IV drug users.
The figure at the base of each bar indicates number of patients.

It is also noteworthy that all of the children with glomerular disease and AIDS in the Miami series were born to mothers using IV drugs (Pardo, personal communication, July, 1988). Therefore, it is possible that some effect of maternal IV drug use was a factor in the development of renal disease in these children. However, in a number of series including the Miami series, there are clearly individuals whose renal disease cannot be attributed to IV drugs. Haitian patients, in whom IV drug use appears to be uncommon, serve as examples (Pape, 1983, 1986; Pardo, 1987). Furthermore, we see only infrequent evidence of significant glomerular disease despite relatively frequent IV drug use in AIDS patients treated in Dallas. It seems, therefore, that there is no simple relationship between IV drug use and the development of glomerular disease in AIDS patients. It is likely that important determinants of the expression of renal disease in AIDS patients remain to be determined. Such determinants will probably relate to host factors (degree of immunosuppression, duration of survival, presence of intercurrent infections or neoplasms) and to properties of the HIV organism itself.

ELECTROLYTE DISORDERS IN AIDS PATIENTS

Electrolyte disorders are common in AIDS patients. Reported disorders now include hyponatremia, hyperkalemia, hypercalcemia and hypocalcemia (Vaziri, 1985; Zaloga, 1985; Jacobs, 1986; Vitting, 1987; Cusano, 1987; Tang, 1988; Southwestern series, 1988). Chief among these is hyponatremia, which occurs in as many as half of hospitalized AIDS patients. There are several potential reasons for this. First, AIDS patients often develop hypovolemia secondary to loss of fluid and sodium from the GI tract. Thus, if the patient consumes hypotonic fluid without adequate replacement of sodium, hypovolemia could limit the delivery of fluid to the distal nephron, thereby reducing the clearance of free water by the kidney. Hyponatremia would ensue. Second, preliminary results suggest that the syndrome of inappropriate ADH can develop in these patients (Vitting, 1987). It would be expected that frequent pulmonary and CNS lesions in AIDS patients predispose the development of SIADH, which would also limit renal excretion of free water. Third, renal tubular retention of sodium may be subnormal in AIDS patients. It is premature to conclude that renal tubular dysfunction occurs frequently in this setting. However, the demonstration of frequent tubular and interstitial lesions in AIDS patients suggests that this could be so. Furthermore, the possibility of infection of renal epithelial cells by HIV might also predispose renal sodium wasting.

Renal wasting of sodium would also be expected in the face of mineralocorticoid deficiency. Indeed, there are reports of adrenocortical dysfunction in AIDS patients (Guenthner, 1984; Green, 1984; Salik, 1985; Bleiwiess, 1986; Membreno, 1987). With this in mind, Membreno and colleagues recently studied the major pathways of adrenocorticosteroid synthesis in patients with AIDS and ARC (Membreno, 1987). These pathways are reviewed in Figure 3.

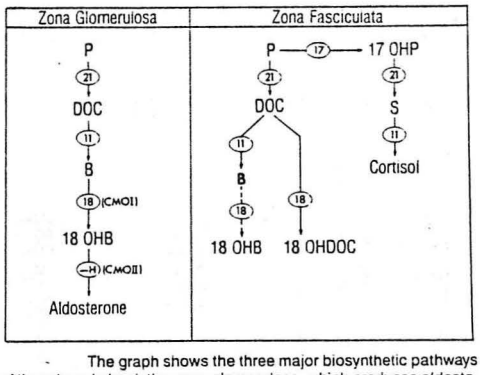


Figure 3:

Pathways of Adrenocorticoid Synthesis. Biglieri (West J Med 148:70, 1988).

The graph shows the three major biosynthetic pathways of the adrenal gland: the zona glomerulosa, which produces aldosterone, and the two major pathways of the zona fasciculata. B = compound B (corticosterone), CMO = corticosterone-methyl-oxidase, DOC = deoxycorticosterone, -H = dehydrogenase, 18-OHB = 18-hydroxycorticosterone, 18-OHDOC = 18-hydroxydeoxycorticosterone, 17-OHP = 17-α-hydroxyprogesterone, P = progesterone, S = 21-deoxycortisol, ◯ = hydroxylase action, — = only active with compound B excess

The pathway leading to the synthesis of aldosterone is situated in the zona glomerulosa, which is under the influence of the renin-angiotensin system. The pathways leading to the synthesis of cortisol and the 17-deoxysteroids (such as deoxycorticosterone [DOC], corticosterone [compound B] and 18-OH DOC) are located in the zona fasciculata, which is under the influence of ACTH and perhaps other substances produced by the pituitary. Membreno et al examined 74 randomly selected hospitalized patients with AIDS and 19 patients with ARC (Membreno, 1987). All patients were clinically stable at the time of study. None was taking glucocorticoids or other drugs that could suppress adrenal function. Their observations are summarized in Table 8 and in Figures 4 and 5.

Table 8: Basal Plasma Steroid Levels in Normal Subjects (NS) and AIDS and ARC Patients.
Membrano et al (J Clin Endocrinol Metab 65:482, 1987)

	NS	AIDS	ARC
Cortisol (nmol/L)	298	433*	295
DOC (pmol/L)	163	245	160
B (nmol/L)	8.9	12.4	10.6
18-OH DOC (pmol/L)	150	115	152
18-OHB (pmol/L)	712	1392	1843
Aldosterone (pmol/L)	236	344	275

* P < 0.01 vs. normal subjects

Table 8 shows that basal plasma levels of adrenal steroids were generally normal in individuals with AIDS or ARC. Average basal cortisol levels were actually slightly increased in patients with AIDS. However, as shown in Figure 4, levels of cortisol and the 17-deoxysteroids were significantly less after acute ACTH stimulation in AIDS and ARC patients compared to normal controls.

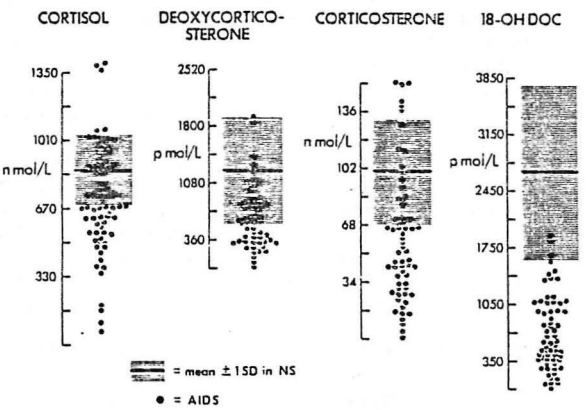


Figure 4:

Plasma Steroid Levels 60 min after Acute ACTH Administration in 74 AIDS Patients.
Membreno et al (J Clin Endocrinol Metab 65:482, 1987). The stippled areas indicate the mean ± 1 SD in normal controls.

Most ARC patients also had subnormal responses to acute ACTH administration, although their suppression of 17-deoxysteroid levels was less than in AIDS patients. The next figure shows the effects of prolonged administration of pharmacologic doses of ACTH in 14 AIDS patients who had subnormal responses after acute ACTH stimulation. Also shown are the effects of prolonged ACTH stimulation in 9 ARC patients.

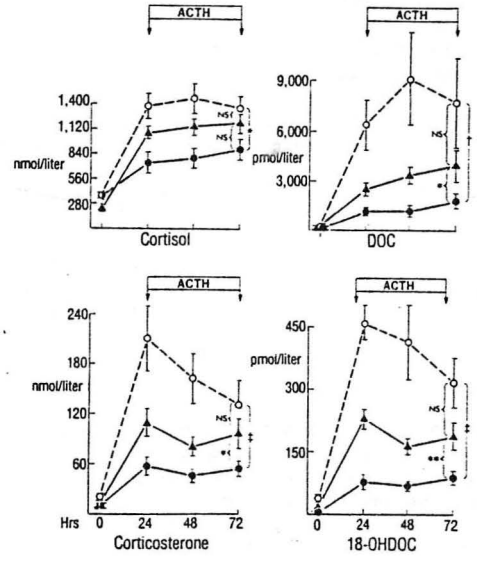


Figure 5:

Plasma steroid levels during 3 days of ACTH administration. Membreno et al (J Clin Endocrinol Metab 65:482, 1987).. Vertical lines indicate 1 SEM. Open circles, normal subjects. Closed circles, patients with AIDS. Triangles, patients with ARC.

In AIDS patients, the mean cortisol level after 3 days of ACTH stimulation was slightly but significantly less than in normal subjects. The levels of the 17-deoxysteroids after 3 days of ACTH were profoundly less than in controls. In ARC patients, levels of cortisol and the 17-deoxysteroids after chronic stimulation were not statistically different from control levels. Four (5%) of the AIDS patients in this series had overt adrenal insufficiency. ACTH levels in these 4 patients were not elevated despite reduced cortisol and aldosterone levels, hyperkalemia and hypotension.

The same investigators also examined the function of the zona glomerulosa. In both AIDS and ARC patients, zona glomerulosa function appeared to be normal as evidenced by appropriate responses of plasma levels of 18-OH corticosterone and aldosterone to provocative stimuli. Thus, although there was no evidence of overt mineralocorticoid deficiency in the patients studied, there was evidence that the function of the zona fasciculata was frequently subnormal, particularly as regards production of the 17-deoxysteroids. Such a pattern is consistent with that seen in some patients with pituitary insufficiency. Two of the AIDS patients with subnormal 18-OH DOC responses to ACTH were shown to have subnormal adrenocorticosteroid responses after administration of corticotropin releasing hormone (CRH). Since these patients had normal plasma cortisol responses to ACTH administration, their abnormal responses to CRH are consistent with the presence of pituitary disease.

It has been noted that adrenal glands in AIDS patients are quite frequently infected by CMV and less frequently by other microbes (Reichert, 1983; Tapper, 1984). Adrenal hemorrhage and infarction can also occur in these patients (Reichert, 1983; Tappen, 1984). In general, such adrenal lesions are patchy and probably do not commonly destroy sufficient adrenal tissue to cause overt adrenal insufficiency. Membreno and colleagues believe it is more likely that pituitary infection by HIV leads to pituitary insufficiency which in turn predisposes adrenal insufficiency. Concomitant involvement of the adrenals by HIV, CMV, mycobacterium avium intracellulare, cryptococci or tumor could then lead to complete adrenal insufficiency. For practical purposes, it must be kept in mind that patients with AIDS often have subclinical adrenal insufficiency. In conditions of stress or when there is extensive infarction of the adrenal, overt adrenal insufficiency can occur. Hyponatremia and/or hyperkalemia may be signs of this. Testing for adrenal insufficiency and appropriate administration of adrenocorticosteroids is warranted in such situations.

The possibilities of hypo- and hypercalcemia have been noted earlier. To date, there is little information regarding PTH and vitamin D levels or the possibility of bone disease in AIDS patients.

APPROACH TO AIDS PATIENTS WITH RENAL DISEASE

Acute renal failure in AIDS patients can be minimized by correcting dehydration and avoiding nephrotoxins whenever possible. It is not always possible to avoid potentially nephrotoxic agents, however. Drugs that require particular caution in this regard include the aminoglycosides, trimethoprim/sulfamethoxazole, pentamidine, amphotericin, ketoconazole and the nonsteroidal antiinflammatory agents. Pentamidine has been associated with azotemia in about one-fourth of AIDS patients receiving the drug, possibly because it tends to cause significant hypoglycemia (Andersen, 1986; Stahl-Bayliss, 1986). Amphotericin is well known to induce renal failure, renal tubular acidosis and nephrocalcinosis. It is noteworthy, however, that most patients developing nephrocalcinosis in our series did not receive this drug. Ketoconazole has been shown to block adrenal steroid synthesis. It should be used with care in AIDS patients who might have compromised adrenal function.

The decision to dialyze AIDS patients with advanced renal failure unresponsive to conservative measures can be a difficult one. There is the potential for recovery of renal function with acute uremia. Hence, support of patients with acute renal failure seems warranted when the patient otherwise has a reasonable chance of extended survival. The decision to initiate dialysis for patients with chronic renal failure is more difficult. Rao et al and others emphasize that AIDS patients with chronic renal failure due to "HIV-nephropathy" fare quite poorly despite aggressive nutritional support and hemodialysis. It is noteworthy, however, that preliminary results from one center do not indicate an adverse effect of renal failure on the survival of AIDS patients (Carbone, 1987). Rao et al recommend that the decision to initiate dialysis "must be individualized, and must take into account the wishes of the patient and family with the guidance of the primary physician and other health care workers" (Rao, 1987).

When hemodialysis is performed on AIDS patients, the CDC recommends the observance of precautions identical to those used for hepatitis patients unless there is a potential for spattering of blood or secretions, when more extensive precautions should be followed (CDC, 1986, 1987b). Current evidence indicates that the rate of HIV infection in health care workers caring for AIDS patients is quite low, that the transmissibility of HIV is much less than for the hepatitis B virus, and that HIV is inactivated by bleach, other sterilizing agents and by desication. Nevertheless, there are a few health care workers who may have contracted HIV infections in the course of caring for AIDS patients (CDC, 1987a). These instances underscore the importance of following precautions recommended by the CDC, especially when there is a potential for contact with HIV-contaminated blood. In this regard, it is notable that the incidence of HIV antibody positivity, as judged by Western blot testing, reaches 10-11% in some chronic hemodialysis centers in New York City and Miami (Reiser, 1988; Ortiz, 1988). Other chronic hemodialysis units in the United States and Europe report rates of 0 to 5% (Goldman, 1986; Baillod, 1986; Baltimore-Boston Collaborative Study Group, 1988; Schmidt, 1988).

CONCLUSIONS

Renal and electrolyte disorders are common in AIDS patients. Among the many such disorders, a particular syndrome characterized by the development of focal and segmental glomerulosclerosis, nephrotic syndrome and rapidly progressive renal failure appears to occur in AIDS patients from certain large urban areas. Whether this syndrome is a specific entity related to HIV infection remains to be established.

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