Transplantation of kidneys between normal mice and mice transgenic of noninfectious HIV

Transgenic kidney in normal mouse

Normal kidney in transgenic mouse

Kidney develops glomerulosclerosis

Kidney remains disease-free

**HIV proteins in glomerulosclerosis.** HIV-associated glomerulosclerosis has been viewed as a complication that occurs either as a direct cellular effect of HIV infection or HIV gene products in the kidney, as an indirect effect of the dysregulated cytokine milieu existing in patients with acquired immunodeficiency syndrome, or both. Studies involving reciprocal transplantation of kidneys between normal and mice transgenic of noninfectious HIV clearly show that the pathogenesis of HIV-glomerulosclerosis is intrinsic to the kidney [176]. In these studies, HIV-glomerulosclerosis developed in kidneys of transgenic mice transplanted into nontransgenic littermates, whereas kidneys from normal mice remained disease-free when transplanted into HIV-transgenic mice [176]. These findings suggest that HIV gene products, rather than infective HIV, may induce the nephropathy either through direct effects on target cells or indirectly through the release of cytokines and growth factors.

**TREATMENT OPTIONS OF GLOMERULOSCLEROSIS ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION**

Antiretroviral therapy
Corticosteroids
Cyclosporine
Angiotensin-converting enzyme inhibitors
Dialysis

**FIGURE 7-35**

Treatment of glomerulosclerosis. There have been no prospective controlled randomized trials of any therapy in patients with nephropathy associated with HIV infection. Thus, the optimal treatment is unknown. Individual case reports and studies, often retrospective, on a small number of patients suggest a beneficial effect of monotherapy with azidothymidine (AZT) on progression of renal disease [177–179]. No reports exist on the effects of double or triple antiretroviral therapy on the incidence or progression of renal disease in patients with HIV who have modest proteinuria or nephrotic syndrome. The incidence of HIV-associated glomerulosclerosis may be declining as a result of prophylaxis with AZT, trimethoprim and sulfamethoxazole, or other drugs. Using logistic regression analysis, Kimmel and colleagues [180] demonstrated an improved outcome related specifically to antiretroviral therapy.

Steroids usually have been ineffective on proteinuria or progression of renal disease in adults and children. Recently, 20 adult patients with HIV-associated glomerulosclerosis or mesangial hyperplasia with proteinuria over 2 g/24 h and serum creatinine over 2 mg/dL were studied. These patients showed impressive decreases in proteinuria and serum creatinine when given 60 mg/day of prednisone for 2 to 6 weeks [181]. Complications of steroid therapy, however, were common. These include development of new opportunistic infections, steroid psychosis, and gastrointestinal bleeding. The short-term improvement in renal function may correlate with an improvement in tubulointerstitial mononuclear cell infiltration [182]. In a single report of three children with perinatal AIDS, HIV-associated glomerulosclerosis, and normal creatinine clearance, cyclosporine induced a remission of the nephrotic syndrome [183]. This report has not been confirmed, and the use of cyclosporine in adults with HIV-associated glomerulosclerosis has not been studied.
Systemic Diseases and the Kidney

**FIGURE 7-36**
Effect of angiotensin-converting enzyme (ACE) inhibitors on progression of glomerulosclerosis associated with HIV infection. Serum ACE levels are increased in patients with HIV infection [184]. Kimmel and colleagues [180], using captopril, and Burns and colleagues [185], using fosinopril, demonstrated a renoprotective effect of ACE inhibitors in patients with biopsy-proven HIV-associated glomerulosclerosis. In the former study, the median time to end-stage renal disease was increased from 30 to 74 days in nine patients given 6.25 to 25 mg captopril three times a day. In the latter study, 10 mg of fosinopril was given once a day to 11 patients with early renal insufficiency (serum creatinine <2 mg/dL). Serum creatinine and proteinuria remained stable during 6 months of treatment with fosinopril. In contrast, patients not treated with fosinopril exhibited progressive and rapid increases in serum creatinine and proteinuria. Similar outcomes prevailed in patients with proteinuria in the nephrotic range and serum creatinine levels less than 2 mg/dL. Captopril also is beneficial to the progression of the nephropathy in HIV-transgenic mice [186]. The mechanism(s) of the renoprotective effects of ACE inhibitors are unclear and may include hemodynamic effects, decreased expression of growth factors, or an effect on HIV protease activity. Renal biopsy early in the course of the disease is important to define the renal lesion and guide therapeutic intervention.

**FIGURE 7-37**
Survival rates in dialysis patients. Once end-stage renal disease (ESRD) develops and supportive maintenance dialysis is needed, the complications of HIV are the dominant factor in patient survival, as they are in patients with HIV infection without renal involvement. Asymptomatic patients on chronic hemodialysis survive longer than do patients with AIDS on chronic hemodialysis. Patients with AIDS also may develop malnutrition, wasting, and failure to thrive that are unresponsive to intensive nutritional support [131]. Recent studies, however, show that the survival of patients with AIDS maintained on chronic hemodialysis is improving. Enhanced survival has been attributed to antiviral drugs, better prophylaxis, and aggressive treatment of opportunistic infections. We have seen four patients with HIV infection survive for more than 10 years on hemodialysis. Chronic hemodialysis and chronic ambulatory peritoneal dialysis are equally appropriate treatments for patients with HIV infection and ESRD. Universal precautions should be used for peritoneal dialysis and hemodialysis alike, because infectious HIV is present in peritoneal effluent and blood.
Renal Disease in Patients Infected with Hepatitis and Human Immunodeficiency Virus

### Predictors of Survival of Patients with Human Immunodeficiency Virus Infection Receiving Chronic Hemodialysis

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<tr>
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<tbody>
<tr>
<td>CD4</td>
<td>0.668</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure, systolic</td>
<td>0.496</td>
<td>&lt;0.02</td>
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<tr>
<td>Infection rate</td>
<td>−0.539</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>−0.537</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Edema +/−</td>
<td>14.5 vs 6.1 mo</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antiretroviral therapy +/−</td>
<td>15.2 vs 62 mo</td>
<td>&lt;0.01</td>
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Predictors of survival. Perinbasekar and colleagues [194] analyzed those factors associated with better survival in patients infected with HIV receiving chronic hemodialysis. A low CD4 lymphocyte count, low systolic blood pressure, increased infection rate, nephrotic range proteinuria, lack of edema, and lack of antiretroviral therapy are associated with decreased survival.

### Recommended Antiretroviral Therapy

- Combination of two reverse transcriptase inhibitors
- Aggressive triple therapy, including a protease inhibitor for patients who are asymptomatic of acquired immunodeficiency syndrome
- Asymptomatic with CD4 <500 cells/µL
- Asymptomatic with CD4 >500 cells/µL but viral load > 20,000

Antiretroviral therapy. Recommended antiretroviral therapy for patients with HIV infection without renal disease includes therapies with two drugs for all patients, combining two reverse transcriptase inhibitors. Aggressive early intervention with triple antiviral drugs, one of which is a protease inhibitor, should be offered to patients symptomatic of AIDS, asymptomatic patients with CD4 counts under 500/µL, and asymptomatic patients with CD4 counts over 500/µL and plasma HIV RNA levels over 20,000 copies/mL [195]. Reduced dosages are required for reverse transcriptase inhibitors in renal insufficiency. Although the clearance information on these drugs is limited, additional dosing is not necessary in patients receiving maintenance dialysis. No dosage reduction is needed for protease inhibitors.

### Other Nephropathies Associated with Human Immunodeficiency Virus Infection

- Immune-complex glomerulopathies
- Proliferative glomerulonephritis
- Membranous glomerulonephritis
- Lupus-like nephropathy
- Immunoglobulin A nephropathy
- Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura

Proliferative glomerulonephritides represent instances of postinfectious glomerulonephritis or manifestations of hepatitis C co-infection [196–199]. Alternatively, proliferative glomerulonephritides may result from renal depository of preformed circulating immune complexes with specificity for HIV proteins and are HIV-associated [199]. In patients infected with HIV, membranous glomerulonephritis has been associated with hepatitis B, hepatitis C, syphilis, and systemic lupus erythematosus [198,200–203]. Lupus-like nephritis has been reported in children and adults with HIV infection in association with membranous, mesangial, and intracapillary proliferative glomerular lesions [204]. IgA nephropathy has been reported in association with HIV infection. The occurrence of IgA nephropathy may not be coincidental and is HIV-associated. Indeed, circulating immune complexes composed of idiotypic IgA antibody reactive with anti-HIV IgG or IgM were identified in two patients, and the identical immune complex was eluted from the renal biopsy tissue of one patient studied [199,205]. Unlike HIV-associated glomerulosclerosis, HIV-associated IgA nephropathy has been reported exclusively in white patients with early HIV infection exhibiting microscopic or macroscopic hematuria, absent or modest azotemia, and slowly progressive disease [206]. Instances of intravascular coagulation related to TTP or HUS are recognized with increased frequency and may be the first manifestation of HIV infection, although most develop at a late stage of the disease. The cause of hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) in patients infected with HIV is unknown. Plasma tissue plasminogen activator is increased in patients infected with HIV who have thrombotic microangiopathy [207]. There is no association with Escherichia coli 0154:H7 infection, and intercurrent infections have been demonstrated in only one third of patients. Renal involvement in TTP usually is minimal, whereas vascular and glomerular involvement are more frequent and extensive in HUS and can lead to renal cortical necrosis. Therapy with plasmapheresis, using fresh frozen plasma replacement, should be instituted as soon as the diagnosis of HIV-related HUS/TTP is made [208].