HIV AND END-STAGE RENAL DISEASE: PRACTICAL ISSUES IN MANAGEMENT

Geoffrey R Bihl, *MB BCh, MMed, FCP (SA)*
Nephrologist and Clinical Director, Winelands Kidney and Dialysis Centre, Somerset West, W Cape

According to UNAIDS data there are 40 million HIV-infected people around the globe. An uncommon complication of HIV is HIV-associated nephropathy (HIVAN), and this condition is expected to be one of the leading causes of end-stage kidney disease (EKD) in black men in the new millennium. Patients present with an immune complex glomerulopathy and focal segmental glomerulosclerosis together with proteinuria and haematuria and occasionally severe hypertension. Peripheral oedema is unusual. In the era before antiretroviral therapy (ART) the median survival in the HIV-infected population on dialysis was 10 months. However, since the introduction of highly active antiretroviral therapy (HAART) and optimal prevention of opportunistic infections, a life expectancy of 10 - 20 years can be expected. Unfortunately patients infected with HIV are often excluded from renal replacement therapy (RRT) programmes despite such encouraging outcomes and despite the fact that the outcome of renal transplantation in HIV patients is comparable to that in HIV-negative recipients at 1-year follow-up in experienced centres. In the South African context HIV/AIDS has an alarming prevalence, although dialysis and transplantation are offered only to very few and often only in the acute state. In the light of the new data, HIV seropositivity (especially when the patient is receiving HAART) needs to be reconsidered as an absolute contraindication to renal replacement.

EPIDEMIOLOGY AND PATHOLOGY

In South Africa a national community-based survey suggests that HIV prevalence in the general population is close to 12% (12.8% in females and 9.5% in males).[1] Equally alarming is the finding that an estimated 15.7% of health workers employed in the public and private health facilities located in four South African provinces are infected with HIV/AIDS.[2] Chronic kidney disease develops in 2 - 10% of patients and risk factors include African descent, male gender, and a concomitant diagnosis of diabetes or hypertension and proteinuria.[3] The development of HIVAN has definitively been linked to renal cellular infection and focal segmental glomerulosclerosis appears to be the commonest glomerular pathology. The fact that the disease typically affects men of African descent has obvious consequences in the South African context.

PRE-DIALYSIS

There appears to be a high prevalence of proteinuria on the first urine analysis obtained after HIV documentation.[4] Early treatment with HAART and angiotensin-converting enzyme (ACE) inhibition may offer long-term renal survival benefits in HIVAN, and in addition some clinicians have used low-dose steroids.

RENAL REPLACEMENT THERAPY

Despite rates of EKD in the general population in South Africa estimated to be about 400 per million population (pmp), only 99 pmp receive RRT.[5] For this reason patients suffering from HIV and EKD are excluded from long-term dialysis programmes. Such exclusions may be based on historical grounds, as previously survival was poor, and on fear of cross-infection to other dialysis patients and dialysis staff. More recently the survival of HIV-positive patients has improved and is often equal to or better than those not infected with HIV.[6]

HAEMODIALYSIS

The risk of nosocomial HIV infection to health workers in the dialysis setting is a concern owing to the nature of needle access for haemodialysis (HD). The risk of infection from percutaneous exposure to infected blood is 0.3%.

Initial misinformation and panic regarding acquisition of HIV created great concern, and extreme precautions against the infection were taken. Dialysis units treating infected patients often resembled a set from a science fiction movie, with staff wearing caps, gowns, masks and booties and most patients being strictly isolated with their own dedicated dialysis machines. Some shared machines with patients infected with highly infectious hepatitis B! The more modern approach proposed by the Centers for Disease Control (CDC) in the USA stresses the adoption of universal blood and body fluid precautions, standard disinfection and sterilisation strategies during dialysis, and careful control of dialyser re-use where practised. Dialysis machines should not be shared between patients with HIV and those infected with hepatitis B, and isolation of HIV-infected patients and dedicated machine use is currently not recommended by the CDC or the National Kidney Foundation (NKF) task force on dialysis.

In the pre-HAART era survival of HIV-infected patients was dismal to the point at which it was an ethical dilemma whether chronic dialysis should be offered to these patients. However, with the use of HAART the survival of HIV-infected patients on dialysis has improved considerably. Importantly however, it has been suggested that HD may activate HIV replication, although considering the potent antiretroviral (ARV) activity of the newer HIV drugs activation of HIV seems unlikely.

PERITONEAL DIALYSIS

Theoretically peritoneal dialysis (PD) poses less risk than HD to dialysis staff and other patients as PD fluid is less infectious than blood. The glucose load provided by PD fluid affords the patient an adequate caloric load, although protein losses may actually worsen the patient's nutritional status. Survival rates are comparable to those for patients receiving HD. Controversy abounds regarding a supposed increased risk of peritonitis, especially when the patient is in an immunocompromised state. Studies have shown increased rates of *Pseudomonas* and fungal infections.[6] Once the expected immune reconstitution on HAART occurs, the risk of peritonitis falls to that in patients not infected with HIV. Adequate disinfection protocols are essential when performing PD as both HIV p24 antigen and HIV antibodies have been found in PD fluid.

Both HD and PD are effective modalities of RRT in the HIV-infected EKD patient. The choice of modality should depend on the individual's lifestyle and availability of adequate family support and medical expertise. A prerequisite is that such patients should receive optimal ART.

HIV seropositivity should not be a negative dialysis criterion. Patients with HIVAN and EKD should be allowed to choose a specific dialysis modality, because it is not a factor in predicting survival.[7] When progression to kidney failure is suspected timely fashioning of an arteriovenous fistula should be considered, as well as the placement of a PD catheter. Temporary HD lines are best avoided in those patients with EKD as long-term vascular access may often be compromised by such catheters.

TRANSPLANTATION

The arguments in favour of transplantation for HIV-infected patients have gained a new impetus with improvement in survival on HAART. In the South African context experience with transplantation in HIV-positive patients is limited. Major issues in this regard include:

- false-positive tests for HIV pre- and post-transplantation
- transmission of HIV infection through the allograft
- outcomes of HIV-positive patients who undergo transplants, and
- acquisition of HIV-infection following transplantation.

Interestingly, immunosuppressive agents such as cyclosporin and tacrolimus may retard replication of HIV virus, and mycophenolate mofetil may potentiate the ARV effect of commonly used HIV drugs.[9]

GENERAL PATIENT MANAGEMENT

ANAEMIA

Anaemia is common in HIV-infected patients with renal disease, and overall anaemia is the commonest haematological abnormality in HIV-infected patients. Mean haematocrit levels in patients with HIVAN are lower than in other patients with end-stage renal disease (ESRD) starting dialysis. HIV infections may exacerbate anaemia in patients with kidney disease by direct effects of HIV infection on erythropoiesis, opportunistic infections, ARV drugs, and other rare mechanisms such as thrombotic microangiopathies. Such anaemia is independent of other factors associated with shorter survival and it should be managed as aggressively, e.g. with recombinant human erythropoietin (EPO), which is utilised for any patient with EKD. HIV-positive patients often require higher doses of EPO to maintain adequate haemoglobin levels. Although rare, parvovirus B19 infection should be suspected if anaemia in the HIV-infected patient does not respond to EPO and other causes have been ruled out. Iron is essential for haemoglobin formation and iron status should be monitored and corrected accordingly by the percent transferrin saturation and serum ferritin levels. In this situation it is important to realise that ferritin levels are often elevated in patients with HIV infection as a marker of inflammation, and high iron stores may also adversely influence outcome in HIV-infected patients. Some studies have shown that oxidative stress and iron may activate HIV-1, and when intravenous administration of iron is carried out, viral loads need to be monitored.

VACCINATION

The immunosuppression that results from HIV infection and uraemia is likely to lead to suboptimal response to vaccination. Immunisation for hepatitis B in HIV-infected EKD patients is important because not only does hepatitis B virus infection occur more frequently in HIV-positive subjects, but these patients also are more likely to develop chronic hepatitis B infection. Unfortunately, however, antibody response to hepatitis vaccination is impaired in HIV-infected patients, only half of whom develop a protective antibody response.[8]

There is a concern regarding the drug-drug interactions between protease inhibitors and calcineurin inhibitors, and vigilant drug level monitoring is imperative.[10] Although relatively few patients with HIV currently undergo organ transplantation, patient and graft survival are comparable to United Network for Organ Sharing (UNOS) figures at 1 year of follow-up. Furthermore, there is no evidence of progression of HIV disease, and as experience grows in this field asymptomatic HIV-infected patients with ESRD may be offered this most optimal of renal replacement therapies.

Adequate and accurate testing of any cadaveric or living allograft for HIV infection, especially in high-risk populations,

reduces the risk of transmission to the recipient although such infections do occur.

An adequately functioning allograft restores sexual and reproductive function in the recipient of any kidney allograft, and in parts of the world where the prevalence of HIV is high (such as in South Africa) HIV infection following transplantation is a real concern.[11]

ISSUES RELATED TO HAART

The aim of ART in EKD patients with HIV should be to reduce the viral load to undetectable levels and to prevent opportunistic infections. With the use of HAART, improved prophylaxis and treatment of opportunistic infections there has been a dramatic improvement in survival of HIV-infected patients, although such therapy is often under-utilised in HIV-infected patients with EKD.[10]

There are three main groups of ARV drugs, nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs) and protease inhibitors (PIs). In most patients a combination of either two NRTIs with a PI or two NRTIs plus one NNRTI are used. NRTIs used in HIV therapy are primarily excreted by the kidneys, so the dose administered to EKD patients is 30 - 50% of the normal dose for various drugs (see Table I). In addition, on dialysis days the NRTIs should be given after dialysis. Abacavir is the only NRTI the absorption, elimination and distribution phases of which are not altered by renal insufficiency and which does not need dose adjustment in patients with ESRD. Since abacavir is mainly metabolised in the liver, the fraction removed during dialysis is not clinically significant, and it can be administered at any time on dialysis days. NNRTIs and PIs are mainly metabolised in the liver by cytochrome P_{450} isoenzymes, and do not need dose adjustments in patients with ESRD. NNRTIs should be administered after haemodialysis to minimise loss during dialysis. In contrast, PIs can be administered regardless of the dialysis schedule. Table I details dosage adjustments of ARV agents required in patients with kidney insufficiency.[12]

Use of ARV drugs is a double-edged sword in that despite their positive antiviral properties their use results in a number of renal abnormalities. Table II details such effects.[13]

TABLE I. ORAL DOSAGE RECOMMENDATIONS FOR ANTIRETROVIRAL DRUGS IN HEMODIALYSED PATIENTS[12]

Drug	Normal dosage	Haemodialysed patients
NRTIs		
Zidovudine*	200 mg tds	100 mg tds
Didanosine*	200 mg bd	200 mg daily
Zalcitabine*	0.75 mg tds	0.75 mg qd
Stavudine*	40 mg bd	40 mg daily
Lamivudine*	150 mg bd	150 mg stat then 250 mg q 24 h
Abacavir*	600 mg bd	Normal dosage
NNRTIs		
Nevirapine*	200 mg daily for 14 days then 200 mg bd	Normal dosage
Delavirdine*	400 mg tds	NA
Efavirenz	600 mg daily	Normal dosage
PIs		
Saquinavir†	600 mg tds	Normal dosage
Ritonavir	600 mg bd	Normal dosage
Indinavir	800 mg bd	Normal dosage
Nelfinavir	750 mg tds	Normal dosage
Amprenavir	1 200 mg bd	Normal dosage

* Drug should be administered after the haemodialysis session.
† When saquinavir is used in combination with ritonavir, its dose should be reduced.

GENERAL MEASURES

Nephrologists and physicians taking care of HIV-infected ESRD patients need to be aware of the special issues relevant to HIV-infected patients with ESRD and should co-operate actively with HIV specialists to improve the outcome and quality of life of this group of patients. Prophylaxis against *Pneumocystis jiroveci* pneumonia, tuberculosis and cyto-megalovirus (CMV) in the transplant patient are imperative, while surveillance and early intervention for Kaposi's sarcoma and other malignancies is also important.

CONCLUSIONS

HIV/AIDS is reaching epidemic proportions in southern Africa. With the positive governmental move towards widespread availability of ARV drugs, clinicians are encouraged to gain a sound knowledge of the effects of these agents in patients with and without kidney failure. RRT should be available for

TABLE II. RENAL ABNORMALITIES INDUCED BY ANTIRETROVIRAL DRUGS[13]

Drug	Abnormality
NRTIs	
Zidovudine	Lactic acidosis, rhabdomyolysis
Didanosine	Lactic acidosis, elevated serum uric acid
Zalcitabine	Acute renal failure, lactic acidosis, hyponatraemia, hypocalcaemia, renal calculi
Stavudine	Lactic acidosis, **raised uric acid**
Lamivudine	Lactic acidosis
NNRTIs	
Nevirapine	Lactic acidosis
PIs	
Saquinavir	Lactic acidosis, hypocalcaemia, **hypo/hyperkalaemia**, magnesaemia and phosphoraemia, pancreatorenal syndrome
Ritonavir	Acute renal failure, pancreatorenal syndrome, hypocalcaemia, **hypo/hyperkalaemia**
Indinavir	Lactic acidosis, intratubular precipitation, urinary lithiasis, renal insufficiency
Nelfinavir	Lactic acidosis, hypocalcaemia, lithiasis

those HIV-positive patients who require dialysis, as HAART, their young age and otherwise good health afford them an excellent long-term prognosis.

REFERENCES

1. Connolly C, Colvin M, Shisana O. Epidemiology of HIV in South Africa – results of a national, community-based survey. *S Afr Med J* 2004; **94:** 776-781.
2. Shisana O, Hall EJ, Maluleke R. HIV/AIDS prevalence among South African health workers. *S Afr Med J* 2004; **94:** 846-850.
3. Szczech LA. Renal diseases associated with human immunodeficiency virus infection: epidemiology, clinical course, and management. *Clin Infect Dis* 2001; **33:** 115-119.
4. Gupta SK, Mamlin BW, Johnson CS. Prevalence of proteinuria and the development of chronic kidney disease in HIV-infected patients. *Clin Nephrol* 2004; **61:** 1-6.
5. Katz I. Kidney and kidney related chronic diseases in South Africa and chronic disease intervention program experiences. *Adv Chronic Kidney Dis* 2005; **12:** 14-21.
6. Rao TK. Human immunodeficiency virus infection in end-stage renal disease patients. *Semin Dial* 2003; **16:** 233-244.
7. Ahuja TS, Collinge N, Grady J. Is dialysis modality a factor in survival of patients with ESRD and HIV-associated nephropathy? *Am J Kidney Dis* 2003; **41:** 1060-1064.
8. Ahuja TS, Kumar S, Mansoury H. Hepatitis B vaccination in human immunodeficiency virus-infected adults receiving hemodialysis. *Kidney Int* 2005; **67:** 1136-1141.
9. Margolis DM, Kewn S, Coull JJ. The addition of mycophenolate mofetil to antiretroviral therapy including abacavir is associated with depletion of intracellular deoxyguanosine triphosphate and a decrease in plasma HIV-1 RNA. *J Acquir Immune Defic Syndr* 2002; **31:** 45-49.
10. Izzedine H, Launay-Vacher V, Baumelou A. Antiretroviral and immuno-suppressive drug-drug interactions: an update. *Kidney Int* 2004; **66:** 532-541.
11. Kahn D, van Rensburg M, Botha JF. HIV infection following transplantation: the South African experience. *Transplant Proc* 2001; **33:** 3649-3650.
12. Izzedine H, Launay-Vacher V, Deray G. Inadequacy of antiretroviral drugs dosage adjustment in HIV patients receiving dialysis. *Kidney Int* 2003; **64:** 2324.
13. Izzedine H, Launay-Vacher V. An appraisal of antiretroviral drugs in hemodialysis. *Kidney Int* 2001; **60:** 821-830.

The *Southern African Journal of HIV Medicine* would like to thank *Specialist Forum* for permission to reprint this article.