

GUIDELINES FOR RENAL REPLACEMENT THERAPY IN HIV-INFECTED INDIVIDUALS IN SOUTH AFRICA

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INDEX

1. Working Group	3
2. Dialysis in HIV positive patients	4
Haemodialysis	5
Peritoneal Dialysis	6
Challenges and recommendations	6
3. Kidney transplantation in HIV positive patients	7
Main recommendations	7
Important considerations	8
Exclusion criteria	8
Source of organs	9
Immunosuppressive protocols	10
Transplant kidney biopsy	10
Psychological assessment and support	10
HAART	10
Special consideration in children	11
4. HIV-related criteria for renal dialysis and transplant programmes	11
5. Appendix I: National Health Guidelines For Chronic Renal Dialysis	12
6. Appendix I1: Dialysis References	15
7. Appendix III: Transplant References	16
8. Appendix IV. Dosage of ART in CKD	18

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1. DIALYSIS IN PATIENTS WITH HIV INFECTION

1.1 Introduction

HIV infection is common in South Africa and presents our society with numerous challenges. HIV can cause chronic kidney disease (CKD) and can contribute significantly to the burden of patients requiring renal replacement therapy (RRT). HIV associated nephropathy (HIVAN) was the third commonest cause of end stage renal failure (ESRF) in black patients in the USA after hypertension and diabetes [1], and since the availability of antiretroviral therapy (ART) is now in 7th place (USRDS, 2006). Furthermore HIV infection may co-exist with end stage renal failure of any other cause and we have even experienced instances of seroconversion to HIV positive of patients already on dialysis.

In South Africa RRT is not freely available. Patients who can afford it or who have medical insurance may be able to receive these expensive therapies in the private sector. For the majority, however this service is not freely available and is provided to a select few in some state hospitals. Patients are selected for dialysis based on state criteria for acceptance to a transplant programme (Appendix 1).

Even if patients with ESRF fulfil the state criteria most centres are limited by the availability of 'slots' for dialysis. These are defined by the institution based on availability of funds, staff and equipment. Because the optimal form of RRT is renal transplantation, dialysis is seen as a bridge to transplant and the state 'criteria' are underpinned by the 'transplantability' of the patient. Any guideline on dialysis would have to keep this approach in mind and the availability dialysis for HIV positive patients will be contingent on our ability to transplant them.

1.2 Dialysis in HIV positive patients.

In the pre-HAART era the survival of most patients with advanced HIV infection was dismal. Similarly for patients with HIV infection on dialysis the outcome was poor even in the developed world.[2] This led some to recommend withholding dialysis from these patients. After the advent of anti-retrovirals however several retrospective studies in Europe and the USA have confirmed survival rates in the short term which are similar to the non-infected non-diabetic population[3]. However predictors of poor outcome include[4]

1. Low CD4 counts
2. High viral loads
3. HIVAN as the cause of ESRF
4. Absence of HAART
5. Opportunistic infections.

Given the finding that survival of HIV positive patients receiving HAART is similar to non-infected dialysis patients it has been recommended by guidelines in both the USA and Britain that dialysis not be withheld from these patients on the basis of their HIV

serostatus. [5, 6] However the survival of HIV positive patients on HAART on dialysis is still worse than that of the general HIV positive population. Studies have shown a more rapid progression of HIV infection in patients with kidney failure and the presence of kidney disease either in the form of proteinuria or a raised creatinine portends a poorer outcome for the patient.[5] This has led to the initiation of transplantation in stable HIV positive patients with encouraging early results.

Both haemodialysis (HD) and peritoneal dialysis (PD) have been employed in these patients. Literature review shows that both maintenance HD and PD are effective modes of RRT in HIV patients with ESRD, although there are some points of concern with both modalities[6, 7].

1.2.1 Haemodialysis

Haemodialysis exposes the dialysis staff to blood products and contaminated needles. The risk of HIV seroconversion after a needle stick injury from an infected patient is estimated to be about 0.3%. In addition, the larger the blood inoculum and the later the stage of HIV infection, the greater the risk of seroconversion. The use of universal precautions is the best form of prevention of nosocomial infection.

Dialysis access in the form of an AV-fistula is the best option for these patients and similar patency rates to the non-infected population have been shown.[6, 8] Some concern has been raised because of higher rates of PTFE graft infection in HIV positive patients especially those with AIDS. This has led some to avoid permanent access if an AVF cannot be successfully created. However the use of temporary catheters and permcaths for long term use often lead to inadequate dialysis, not to mention the risks of infection, vascular occlusion and bleeding. HIV transmission in a dialysis unit has been documented via inadequate sterilization of re-used needles.[9, 10] Other infections have been caused by breaks in universal precautions and infection control procedures. Guidelines for infection control and machine disinfection set by the Association for the Advancement of Medical Instrumentation and CDC should be adhered to at all times.

1.2.2 Peritoneal dialysis (CAPD)

Theoretically there is less exposure of staff to HIV with PD than with HD because peritoneal fluid is much less infectious than blood, there is less likelihood of needle stick, and the nature of staff to-patient contact is different. HIV was shown to survive in PD effluents at room temperature for up to seven days and in PD exchange tubings for up to 48 h. Both sodium hypochloride 50% (Amukin), and household bleach 10% solutions, in dilutions of 1:512, are effective in killing HIV in dialysate. Patients need to be educated on the need to properly dispose of these fluids. Peritoneal dialysis patients should be instructed to pour dialysate into the home toilet and to dispose of dialysate bags and lines by tying them in plastic bags and disposing of the plastic bags in conventional home garbage[6, 11].

CAPD may aggravate the malnutrition and hypoalbuminemia in HIV patients with severe wasting syndrome. The rate of peritonitis has also been higher in patients with low CD4

counts in the pre-HAART era. Both gram positive infections and Pseudomonas infection as well as fungal infections have been reported as being more common [11].

Overall, given the fact that outcome does not seem to depend on modality of dialysis the choice of RRT in HIV-infected patients should be based on an individual patient's lifestyle, preferences and availability of family and other support, and not on HIV seropositivity. In South Africa the dialysis modality offered will be further restricted by availability.

The substantial population prevalence of HIV infection (estimated at 6 million), even at a best case scenario of prevalence of HIVAN at 1% of the infected population would mean that 60 000 individuals would face this condition that rapidly progresses to ESRF without appropriate care. That comes to almost 1200 patients per nephrologist! If only (conservatively again) 10% progressed to ESRF this would mean an additional 6000 individuals requiring dialysis -this is more than the current dialysis population in South Africa!

1.3 Challenges and Recommendations

1. Early detection of CKD and prevention of progression to ESRF is of prime importance. The importance of routine screening for kidney disease and appropriate early referral cannot be stressed enough. Evidence indicates that treatment with HAART, ACE-inhibitors and possibly steroids may slow or arrest the progression to ESRF[6]. Early detection also allows for counselling and preparation of patients for RRT. This includes early initiation of HAART, exploring options for RRT, allowing patients to acquire a medical aid, pre-emptive transplantation and access creation.
2. Co-infection of these patients with Hepatitis B and C may contribute to the burden of renal disease and also complicates therapy. Adequate diagnosis will allow for treatment
3. Drug rollout issues-To allow adequate access to dialysis the availability of ARVs to patients with ESRF must be prioritized.
4. Opportunistic infection's and malignancies in patients with extremely low CD4 may preclude transplantation This is especially so with certain infections like cryptococcosis or disseminated Kaposi's sarcoma. (See HIV transplantation guidelines and Department of Health guidelines for other contraindications to renal transplantation).
5. Based on current data we cannot justify excluding patients with HIV infection from receiving dialysis. Patients who are stable on HAART at the time of ESRF should not be treated any differently to other patients whatever the cause of the ESRF. Similarly, patients in whom HIV infection is coincidental should be started on HAART as soon as possible and dialysis should not be withheld. Patients with advanced HIV disease who present acutely ill will need to be assessed on an individual basis to determine if dialysis will be offered. This will depend on the following considerations
 - i. Does the patient have acute reversible renal failure ?
 - ii. What is the short term prognosis of the patient?
 - iii. What is the availability of treatment at the centre?

- iv. Would the patient be able to re-constitute his immune system? This may depend on several things including CD4 count, previous HAART, compliance and disease complications.
- v. Does the patient have a contraindication to renal transplantation eg lymphoma

2. GUIDELINES FOR MANAGEMENT OF KIDNEY TRANSPLANTATION IN HIV INFECTED PATIENTS

2.1 Introduction

Prior to the introduction of HAART therapy the morbidity and mortality of HIV-infected patients was considered too high to justify using scarce resources in transplanting infected patients. There were concerns that immunosuppression may accelerate HIV replication and result in rapid progression of the disease and increased mortality. Most reports on the effects of immunosuppressive agents (cyclosporine and mycophenolate mofetil) in vitro, on non-transplant HIV infected patients and in HIV infected transplant patients has not shown detrimental affects and have in fact suggested that there may be beneficial effects.

2.2 Main recommendations

All HIV infected patients withCKD should be considered for RRT including dialysis and transplantation.

Before listing for transplantation HIV infected patients must demonstrate:

1. Stability on HAART therapy with good adherence to treatment for at least 6 months
2. Absence of current AIDS defining illness
3. CD4 count >200 for more than 6 months
4. Paediatric criteria:
 - < 1 year of age – aim to get to 1 year or 10kg before transplantation if possible
 - 1 – 6 years CD4% > 25% (but also consider absolute count)
 - > 6 years – CD4 > 200
5. Undetectable viral load (<50 copies/ml) for more than 6 months

2.3 Important considerations

It has been well established that compliance with medication and clinic attendance is essential for successful management of both HIV infection and kidney transplantation. It is recommended that:

1. Patients must be able and willing to attend close and regular follow up
2. Patients must be willing to comply with anti-viral and anti-fungal prophylaxis regimens
3. Patients must have a negative pregnancy test and be willing to use effective contraception
4. Adolescents will need extra support

5. Patients need to agree to be sent to a centre where a multidisciplinary approach including HIV specialists, nephrologists, dietitian and pharmacology support is available.

2.4 Exclusion criteria

1. Advanced cardio-pulmonary disease
2. Active uncontrolled malignancy with reduced life expectancy(see National Guidelines for Solid Organ Transplantation)
3. Significant infection which may flare up or reactivate with immunosuppression (aspergillosis and other fungal infections, severe bacterial disease and active TB)
4. Active Human Papilloma Virus infection
5. Evidence of liver cirrhosis (especially if co-infected with HepB or HepC virus)
6. Untreated Hepatitis B or Hepatitis C co-infection with active viral replication - consider treatment for Hepatitis B or Hepatitis C first
7. Documented progressive multifocal leukoencephalopathy
8. Active Kaposi's Sarcoma or evidence of visceral involvement
9. EBV and HHV8 associated lymphoproliferative diseases
10. Active CMV
11. Documented poor compliance

2.5 HIV-related criteria for renal dialysis and transplant programmes

HIV infection should not be an exclusion from renal dialysis or renal transplant programmes per se. However, like patients with other medical conditions the patient who is HIV-infected with ESRD needs to be assessed in terms of co-morbidities and psychosocial factors for suitability for these programmes.

Renal transplant should only be undertaken in HIV-infected patients when the following criteria are met, in order to optimize the outcome after transplantation:

- 1) Patient on antiretroviral therapy (ART) for at least 6 months
- 2) Adherence to ART is demonstrated and there is a commitment to lifelong therapy
- 3) CD4 count > 200 cells/mm³
- 4) HIV viral load undetectable
- 5) No active opportunistic infections (OIs). If the patient has had a WHO Stage 4 infection or TB they should have been fully treated and have been asymptomatic from this infection for at least 6 months.
- 6) No history of malignancies. However, if the patient has had a previous solid tumour that has been adequately treated and is now in remission they may be considered if they meet criteria for sufficient duration of remission prior to transplantation set out in separate guidelines as for HIV-uninfected patients (consult IPTTR prelisting).

- 7) Absence of certain HIV-related conditions:
- a. History of progressive multifocal leucoencephalopathy (PML)
 - b. History of EBV or HHV 8 associated lymphoproliferative disorders (lymphoma and multicentric Castleman's disease)
 - c. History of visceral Kaposi's sarcoma
 - d. Current advanced human papillomavirus-associated cervical or anal intra-epithelial neoplasia or carcinoma-in-situ.

Where resources are limited these are the most appropriate patients to consider for dialysis programmes as well. However, where resources permit, even HIV-infected patients who do not fulfill the CD4 and viral load criteria or have had recent OIs, but are committed to starting ART and maintaining adherence, may be considered for dialysis. The majority of such patients will subsequently fulfill these criteria when on ART (and opportunistic infections have been treated).

In addition, in patients with the conditions described in 7 b) and 7 c) who are in remission transplantation with subsequent immunosuppressive therapy is inappropriate, but chronic dialysis should be offered for ESRD where possible. This also applies to those with current advanced human papillomavirus-associated cervical or anal intra-epithelial neoplasia or carcinoma-in-situ (7 d)) in whom transplant could be considered once these conditions have been optimally managed.

2.6 Source of organs

Most units are using both cadaver and live related donors. Because most studies have shown nearly equivalent graft and patient survival with HIV-infected vs non-infected recipients, exclusion of HIV patients from the cadaver list cannot be justified. Patients should be encouraged to use live related or unrelated donors wherever possible. It is generally accepted and essential that live donors are fully informed regarding the recipients HIV status.

It is not currently considered safe to use HIV-infected donors but little data is available.

2.7 Immunosuppressive protocols

2.7.1. Induction

Most studies have shown that HIV-infected patients have at least as frequent and more acute rejection than non-HIV recipients. They should all be considered "high immunological risk". It is considered safe to use monoclonal antibodies (basilixumab or dacluzimab) but polyclonal antibody induction therapy (OKT3) should be avoided. Some studies have had beneficial outcomes using Thymoglobulin.

2.7.2. Maintenance protocols

It is generally believed that the apparent anti-HIV effects of cyclosporine and mycophenolate mofetil make these preferred first line immunosuppression together with standard doses of prednisone.

Sirolimus, tacrolimus and azathioprine have been used but there is very little literature available to support using them as first line immunosuppression.

Because of interactions between immunosuppression and antiretroviral drugs, regular drug level monitoring is essential. Once a stable immunosuppressive dose has been achieved the HAART therapy should only be changed under careful supervision.

2.7.3. Acute rejection

A transplant renal biopsy should be considered in all cases of suspected rejection. Standard high dose/short course corticosteroid therapy is considered optimal treatment for acute rejection.

2.8 Transplant kidney biopsy

Many transplant units consider it essential to perform protocol biopsies and units should inform potential recipients before the transplant that this policy may be adopted. Early biopsy may be indicated for delayed graft function or following acute decline in renal function but protocol biopsies should be considered at 1, 3 and 12 months.

2.9 Psychological assessment and support

All potential recipients should have a full psychological assessment and identified problems should be managed appropriately. Following the transplant -the recipient, live donor and family may also need further support – especially true in adolescent patients.

2.10 HAART

Patients must be continued on full therapy following the transplant. It is essential that the transplant unit work with the HIV physician to ensure correct use of all drugs.

Protease inhibitors (PI's) significantly affect metabolism of cyclosporine, tacrolimus and sirolimus requiring dose reduction and increases time intervals.

Efavirenz increases transplant drug requirements.

Some drugs are antagonistic with mycophenolate and the combination may result in reduced anti-viral effects. D4T and AZT are generally avoided.

Atazanavir is also usually avoided because of the frequent use of PPI for acid suppression. Several published guidelines exist describing interactions between drugs commonly used in HIV positive recipients and immunosuppressants.

2.11 SPECIAL CONSIDERATION IN CHILDREN

- Adequate vaccination in children – especially live virus vaccines - prior to transplantation.
- INH prophylaxis in high risk TB areas- this may also apply in adults and is not without controversy.

APPENDIX I: National Health Guidelines For Chronic Renal Dialysis

INTRODUCTION

It is the aim of the health services of South Africa to provide all South African citizens and permanent residents equitable access to chronic renal dialysis. Dialysis is a method of removing waste products from the body for patients with kidney failure. The settings where dialysis is undertaken are: Hospitals, satellites units and homes.

These guidelines must therefore be used to make efficient use of limited resources and assist clinicians to decide who should be accepted onto the programme and who should not. Patients who do not satisfy these criteria but who are nevertheless accepted on to a chronic renal dialysis programme in the private sector, should remain the responsibility of the private sector. Kidney transplantation is the choice for many patients, about a third are not suitable for transplantation and the supply of donor organs is limited.

However, due to the lack of resources, it has to be accepted that there is a need to set boundaries for medical treatment, including renal dialysis.

OBJECTIVES:

The main objectives of the guidelines are as follows:

- i. To optimize the use of scarce resources.
- ii. To promote cost- effectiveness.
- iii. To promote public/private partnership.
- iv. To improve services to users

1. PRINCIPLES

Unlike the public sector, renal transplantation should not be the major criterion for acceptance for chronic dialysis in the private sector.

Individual patients with diabetes and patients with acceptable co-morbid conditions may be considered for long- term renal dialysis although research shows that they do not respond well in the long term.

Patients who satisfy the set criteria and are accepted onto a chronic dialysis programme in the private sector should remain the responsibility of the private sector provider unless there is timeous and specific agreement between the public and private sector to shift the responsibility.

Treatment options for chronic dialysis should be discussed with the patient and the family. They should be allowed to choose the technique that is optimal for the patient with due consideration of medical, social and geographic factors. Treatment that is offered should be cost-effective. In order to make informed choice the potential impact on the patient's life and that of the families should be explained.

Physical and psychological symptoms related to chronic renal dialysis should be treated appropriately and monitored.

Public Private Partnerships should be encouraged as a model for service delivery in chronic renal dialysis.

The service providers must take reasonable measures, within its available resources, to achieve the progressive realization of the services to be offered.

2. Exclusion rather than inclusion criteria should be applied for the selection of a suitable patient.

Before it is decided that dialysis is a suitable option for an individual there should be a full assessment of the patient's healthcare needs such as economic, social, school and work circumstances. The consequences of long- term dialysis are significant on the patient and their families.

2.1 *Medical exclusion criteria*

- i. Active, uncontrollable malignancy or with short life expectancy
- ii. Advanced, irreversible progressive disease of vital organs such as:
 - cardiac, cerebrovascular or vascular disease
 - advanced cirrhosis and liver disease
 - medically or surgically irreversible coronary artery disease
 - lung disease
 - unresponsive infections e.g HPV, Hepatitis B and C

2.2 HIV and AIDS are not a medical exclusion criteria provided the patient has access to a comprehensive AIDS treatment plan including antiretroviral treatment and stable for at least six months and the above exclusion factors are absent.

2.3 Age (provided above exclusion factors are absent) is not a contra-indication for chronic renal dialysis. In the UK the median age of starting renal replacement therapy is 63 years and the median age of the population is 54 years.

2.4 *Psychological Exclusion Criteria*

- (i) Any form of mental illness that has resulted in diminished capacity for patients to take responsibility to their actions.
- (ii) Active substance abuse or dependency including tobacco use.
- (iii) Obesity

2.5 *Compliance*

Patients with proven habitual non-compliance with dialysis treatment and lifestyle modification will be excluded or removed from chronic renal dialysis programme.

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APPENDIX IV. Dosage of ART in CKD

Table 3. (Continued.)

Antiretroviral drug, dosing category	Dosage	Rating ^a	Reference(s)
Tenofovir		B-II	[128, 129]
Usual dosage	300 mg po q.d.		
Dosage for patients with CKD or ESRD			
Creatinine clearance \geq 50 mL/min	No adjustment		
Creatinine clearance 30–49 mL/min	300 mg po q48h		
Creatinine clearance 10–29 mL/min	300 mg po q72h		
Receiving hemodialysis	300 mg po every 7 days ^c		
Receiving peritoneal dialysis	Unknown, use with caution		
Emtricitabine/tenofovir		C-III	[130]
Usual dosage	200 mg/300 mg po q.d.		
Dosage for patients with CKD or ESRD			
Creatinine clearance \geq 50 mL/min	No adjustment		
Creatinine clearance 30–49 mL/min	One tab po q48h		
Creatinine clearance <30 mL/min	Unknown, should not use combination tablet		
Nonnucleoside reverse-transcriptase inhibitors			
Nevirapine		B-II	[131–135]
Usual dosage	200 mg po b.i.d.		
Dosage for patients with CKD or ESRD			
Creatinine clearance >20 mL/min	No adjustment		
Receiving hemodialysis	No adjustment ^c		
Receiving peritoneal dialysis	Unknown, use with caution		
Efavirenz		C-III	[136–138]
Usual dosage	600 mg po q.d.		
Dosage for patients with CKD or ESRD	No adjustment		
Delavirdine		C-III	[139]
Usual dosage	400 mg po t.i.d.		
Dosage for patients with CKD or ESRD	No adjustment		
Protease inhibitors			
Indinavir		C-III	[140, 141]
Usual dosage	800 mg po t.i.d.		
Dosage for patients with CKD or ESRD	No adjustment		
Saquinavir soft gel		C-III	[132, 142, 143]
Usual dosage	1200 mg po t.i.d.		
Dosage for patients with CKD or ESRD	No adjustment		
Saquinavir hard gel		C-III	[132, 142, 144]
Usual dosage	600 mg po t.i.d.		
Dosage for patients with CKD or ESRD	No adjustment		
Nelfinavir		C-III	[133, 145, 146]
Usual dosage	1250 mg po b.i.d.		
Dosage for patients with CKD or ESRD	No adjustment		
Amprenavir		C-III	[147]
Usual dosage	1200 mg po b.i.d.		
Dosage for patients with CKD or ESRD	No adjustment		
Fosamprenavir		C-III	[148]
Usual dosage	1400 mg po q.d./700 mg po b.i.d.		
Dosage for patients with CKD or ESRD	No adjustment		
Ritonavir		C-III	[135, 142, 149]
Usual dosage	600 mg po b.i.d.		
Dosage for patients with CKD or ESRD	No adjustment		

Table 3. (Continued.)

Antiretroviral drug, dosing category	Dosage	Rating ^a	Reference(s)
Atazanavir		C-III	[152]
Usual dosage	400 mg po q.d.		
Dosage for patients with CKD or ESRD	No adjustment		
Entry/fusion inhibitors			
Enfuvirtide		B-II	[153]
Usual dosage	90 mg sc b.i.d.		
Dosage for patients with CKD or ESRD			
Creatinine clearance \geq 35 mL/min	No adjustment		
Creatinine clearance <35 mL/min	Unknown, use with caution		

^a The rating is for the recommendations on dose adjustment for patients with reduced renal function.

^b Zidovudine/lamivudine (Combivir; GlaxoSmith Kline) should be administered as separate component medications in patients with creatinine clearance <50 mL/min.

^c Administer either the daily dose or one of the daily doses after hemodialysis.

^d Zidovudine/lamivudine/abacavir (Trizivir; GlaxoSmith Kline) and lamivudine/abacavir (Epzicom; GlaxoSmith Kline) should be administered as separate component medications in patients with creatinine clearance <50 mL/min.

