GUIDELINES FOR KIDNEY TRANSPLANTATION IN PATIENTS WITH HIV DISEASE

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Levels of evidence:

I = Meta-analysis or RCT

II = Other good quality trial

III = Observational studies/ Case Reports

IV = Expert Opinion

1.0 Key Recommendations:

1. Any patient with end-stage renal disease is eligible for transplantation if medically fit. Life expectancy of at least five years is considered appropriate before embarking on transplantation. (III).

HIV specific inclusion criteria (III)

2. a. CD4 ≥ 200 cells/microlitre for at least six months
   b. Undetectable HIV viraemia (< 50 copies/ml) for at least 6 months
   c. Demonstrable adherence and a stable HAART regimen for ≥ 6 months
   d. Absence of AIDS defining illness following successful immune reconstitution after HAART
   e. Available anti-retroviral treatment options in the future (this must be discussed and confirmed with the treating HIV physician)

Other inclusion criteria (III):

3. a. No evidence of cirrhosis on liver biopsy if co-infected with HBV or HCV. For other stages of liver fibrosis, HBV should be treated prior to transplantation. HCV treatment should be considered after discussions with the hepatologists/co-infection teams (III).
   b. Able to and willing to use contraception
   c. Willing to attend for close follow-up
   d. Negative B-HCG pregnancy test for females
   e. Willing to comply with anti-fungal and antiviral prophylaxis as required, and as per local protocol
   f. In its current state, transplantation in the setting of HIV infection is still considered 'experimental' and therefore the patient must be able to give informed consent (see sample consent form appendix A)

Exclusions

4. a. Previous or current infections that are at high risk of re-activating with immune suppression

   b. Advanced cardiopulmonary disease

   c. History of neoplasms except solid tumours adequately treated and disease free survival documented for > five years (consult IPTTR pre-listing)

   d. HTLV-1 positive patients

   e. Patients with significant human papilloma virus (HPV) associated cervical and anal disease including CIN/AIN III and carcinoma *in situ*.

   f. Hepatic Cirrhosis (F4 fibrosis by Metavir if HBV/HCV co-infection)

   g. Evidence of active viral replication if co-infected with HBV/HCV.

   h. Pregnancy

HIV-disease specific exclusions

5. a. Documented history of progressive multifocal leukoencephalopathy (PML)

   b. Extracutaneous Kaposi's Sarcoma (KS)

   d. EBV and HHV8 -related lymphpoproliferative disorders – lymphomas and multi-centric Castleman's disease

   e. CD4 count < 200 cells/microlitre

   f. Persistent HIV viraemia despite HAART

   g. Continuing non-compliance with anti-retroviral therapy

   h. More than three-class HIV resistance and lack of future HIV treatment options

These criteria may change as we gain in experience and more data emerges

6. Live donation (whether related or unrelated) is preferable to cadaver donation. However, live donors must always be informed of the recipients HIV status. UK guidelines will be adhered to in the assessment of all living donors (II).

Pre-transplant assessment and vaccination.

7. Evidence of current vaccine induced or natural immunity to: Pneumococcus, *Haemophilus influenzae* B, Meningococcus, Influenza, VZV, Hepatitis A and, Hepatitis B(for HBsAg, HBcAb, negative patients).
8. Baseline ophthalmology review to exclude active CMV retinitis and cervical and anal smears for HPV related CIN and AIN (II)

Immunosuppressant Protocols

9. Because of the interactions between immunosuppressants and antiretrovirals, patients selected for transplant should have a trial of four weeks of calcineurin inhibitors (CNI) and mycophenalate (MMF) immune suppression with therapeutic drug monitoring pre-listing to determine the optimal dose of immune suppressants and PIs/NNRTIs on stable HAART. Once optimum doses have been decided, HAART therapy must not be changed without consultation with the transplant and HIV teams (II).
10. Post-operation immune suppression will be according to local guidelines but should be at the level of a 'high risk' recipient (III)
11. Polyclonal antibodies or OKT3 should not be used for induction or rescue (III)

Acute Rejection

11. Bolus therapy with high-dose Methylprednisolone is the treatment of choice. Consider graft nephrectomy after two or more episodes of acute rejection (II).
12. Consider renal transplant biopsy for all episodes of graft dysfunction (IV).

Allograft function

13. Kidneys with delayed graft function should be biopsied as soon as safe (within the first week) and weekly thereafter until function improved (III).
14. Protocol biopsies are considered important in this complex setting and should be considered at 1 month, 3 months and 12 months (III)

Psychological Support

15. Ensure psychological support is available before and after transplantation (III)

2.0 Audit Standards

1. All patients meeting the criteria for renal transplantation as defined in these guidelines should be discussed with and referred to a renal transplantation centre and this should be documented in their case-notes.

2. All patients considered for transplantation should be included on a national database once this is in place.

3.0 Background

With the advent of highly active anti-retroviral therapy (HAART), there has been a considerable improvement in the prognosis of patients with HIV disease [1, 2]. End-stage renal disease (ESRD) is common in the context of HIV infection [3] and is multi-factorial. Diseases, unrelated to HIV directly, including immune complex and hepatitis C associated glomerulonephritis, diabetes mellitus, polycystic kidneys and obstructive nephropathy may be encountered. However, HIV-associated nephropathy (HIVAN) is the commonest cause of ESRD in HIV-infected patients [4,5] and is the third commonest cause of ESRD in black patients in the USA [5].

As a consequence of widespread and increasing use of HAART in the developed world, the incidence of HIVAN may be decreasing, but the number of patients on dialysis programmes both in the USA and across Europe [3] are on the increase. In the pre-HAART era haemodialysis was associated with reduced survival [6]. In the era of HAART, although overall survival and morbidity for HIV-positive patients on dialysis has improved, it is far less than patients not on dialysis programmes [7]. This coupled with the complexities of antiretroviral therapy dosing in patients with reduced renal clearance and dialysis, has prompted consideration of renal transplantation for this group of patients.

Up until recently HIV infection was considered an absolute contraindication to renal transplantation across the majority of transplant centres in the USA [8]. The European Best Practice Guidelines document also considered HIV as an absolute contraindication to renal transplantation [9].

The earlier concerns about additional immunosuppression and its effect on HIV replication and risk of further opportunistic infections have been allayed with increasing experience from a number of centres offering renal and liver transplants to stable HIV-

positive patients [10]. Results from a number of published experiences suggest graft and patient survival comparable to non-HIV infected recipients of both cadaveric and live-related donor kidney transplants [11-17]. Recent guidelines from UK Transplant do not consider HIV infection an absolute contra-indication [18].

There are still a number of issues that need addressing, including the long-term survival of grafts and recipients, the long-term impact of immunosuppression on HIV reservoirs and CD4 cells, and the pharmacokinetic interactions between antiretroviral and immnosupressant therapies. Many of these questions will be answered with increasing experience and well-designed studies [10, 19].

These guidelines have been developed to reflect previous experience of renal transplantation in HIV-positive patients and to maximise patient and graft-survival. As we gain in experience, it is likely that these guidelines will be updated.

In order to make the learning curve as steep as possible it is essential that a national network and registry is set up to develop clinically useful protocols in the shortest space of time.

4.0 Indications for transplantation

The indications for renal transplantations in HIV positive patients are broadly the same as in non-HIV infected patients, that is, any patient with end-stage renal disease is eligible for transplantation [9,18], if medically sufficiently fit. A life expectancy of at least five years is considered appropriate before embarking on transplantation.

4.1 HIV specific inclusion criteria:

There are specific conditions that the patient must meet, in terms of their HIV diseases. These are based on previous experiences with renal transplantation in HIV-positive patients in the pre-HAART [11] and HAART era [14, 16, 17] and include:

a) CD4 $\geq$ 200 cells/microlitre for at least six months

b) Undetectable HIV viraemia (< 50 copies/ml) for at least 6 months
c) Demonstrable adherence and a stable HAART regimen for ≥ 6 months
d) Absence of AIDS defining illness following successful immune reconstitution after HAART
e) Available anti-retroviral teatment options in the future (this must be discussed and confirmed with the treating HIV physician)

4.2 Other criteria:

a) No evidence of cirrhosis on liver biopsy if co-infected with HBV or HCV. For other stages of liver fibrosis, HBV should be treated prior to transplantation. HCV treatment should be considered after discussions with the hepatologists/co-infection teams (III).

It has become increasingly evident that there is an increased mortality, associated with accelerated progression to end-stage liver disease in post renal transplantation in patients with HCV [20] and HBV [21] co-infection. Patients with replicating HBV (positive HBV DNA in blood) should be treated with nucleoside/nucleotide analogues (lamivudine/emtricitabine and tenofovir, which must be part of, or additional to, the HAART regimen to render them aviraemic prior to transplantation and with continued suppressive therapy post-transplantation. Doses need to be adjusted for renal function. In the context of HCV, evidence of replicating HCV (HCV RNA positive by RT-PCR in blood) is considered a contraindication. HCV treatment with pegylated-interferons and ribavirin should be considered in such patients. Patients who have achieved a sustained virological response (negative HCV RNA by RT-PCR 24 weeks after the end of treatment) would be eligible for transplantation.

b) Able to and willing to use barrier contraception
c) Willing to attend for close follow-up
d) Negative B-HCG pregnancy test for females
e) Willing to comply with PCP, CMV, herpes and fungal prophylaxis as required and as per local protocol

f) In its current state, transplantation in the setting of HIV infection is still considered 'experimental' and therefore the patient must be able to give informed consent (see sample consent form appendix A, but note section 5.0 below). Each centre's consent form needs to be adapted accordingly).

4.3 Exclusions

Many of the general criteria applicable to non-HIV renal transplant waiting lists also apply. Infectious complications following solid organ transplantation are common [22] and often life or graft threatening. Re-activation following immune suppression may occur with previously indolent infections, and therefore many of the infections listed below are considered contraindications to listing patients on solid organ transplant lists [19]. As cardiovascular disease is the main cause of mortality after transplantation, it is mandatory to detect and treat symptomatic coronary artery disease, congestive cardiac failure due to valvular disease or cardiomyopathy, and constrictive pericarditis [23]. Patients with advanced cardiopulmonary disease should be excluded. Solid organ transplant recipients are at high risk of occurrence of cancers including human papilloma virus associated cervical and anal carcinomas [24]. For treated solid organ cancers, a variable period of recurrence free survival is required before listing. Recommendations and advice may be obtained from the IPTTR (Israel Penn Transplant Tumor Registry) [http://www.ipittr.uc.edu/Publications/public.cfm].

The following should be considered absolute contraindications:

a) Previous or current infections that are at high risk of re-activating with immune suppression:
    - Aspergillus – infection or colonisation
    - Any multi-resistant fungal infections
    - Cytomegalovirus (CMV) disease with any activity and unresponsive to first line therapy
    - Influenza or RSV infection within 30 days

- Active bacterial infections
- Mycobacterial infections – unless there is clear evidence of successful treatment

b) Advanced cardiopulmonary disease
c) History of neoplasms except solid tumours adequately treated and disease free survival documented for > five years (consult IPTTR pre-listing)
d) HTLV-1 positive patients
e) Patients with significant human papilloma virus (HPV) associated advanced cervical and anal intraepithelial neoplasia (CIN/AIN III) and carcinoma *in situ* need to be excluded
f) Hepatic cirrhosis (F4 fibrosis by Metavir if HBV/HCV co-infection) and evidence of active viral replication if HBV/HCV co-infected
g) Pregnancy
h) Continuing use of illicit recreational drugs

4.4 HIV-disease specific exclusions:

Although prophylaxis is available for many of the common infections resulting from immune suppression, there are certain infections like HHV8 and JC virus for which this is not an option. Early evidence from a pilot transplant programme suggests progression of aggressive Kaposis's Sarcoma (KS) only in patients with pre-existing extracutaneous disease [25]. Patients with low CD4 counts, persistently detectable HIV viraemia and patients with continued non-adherence to anti-retroviral therapy and multi-resistant HIV infection are unlikely to benefit from transplantation.

- Documented history of progressive multifocal leukoencephalopathy (PML)
- Extracutaneous Kaposi's Sarcoma (KS)
- EBV and HHV8-related lymphoproliferative disorders (Lymphoma and multi-centric Castleman's syndrome)
- CD4 count < 200 cells/microlitre
- Persistent HIV viraemia despite HAART

- Continuing non-compliance with anti-retroviral therapy
- More than three-class HIV resistance and lack of future HIV treatment options

These criteria may change as we gain in experience and more data emerges.

5.0 Cadaveric versus live-donor graft

Live donation (whether related or unrelated) is preferable to cadaver donation. However, live donors must always be informed that this is an 'experimental' or 'new' procedure and that the prognosis for graft and patient survival may be significantly less than average. Although individual units and ethics committees may differ in their views, many would currently consider that the donor is fully informed that the recipient is HIV-infected. If this is the case at your centre, then the consent form needs to be adapted accordingly. Thus, if felt appropriate and according to local guidelines, then it is the responsibility of the recipient rather than the medical team to fully inform the donor of their HIV status. UK guidelines [26] will be adhered to in the assessment of all living donors.

HIV-positive patients awaiting transplantation may be blood group B or of African descent and as such well-matched kidneys may not become available. Nevertheless patients should be listed for a DR identical graft. Until experience has increased with transplantation in HIV +ve recipients, extended criteria donors should not be used.

6.0 Pre-transplant assessment and vaccination

Because of the increased risk of infectious complications post-transplant we would recommend the following minimal vaccinations (if previously unvaccinated) and assessments for pre-transplant immunity:

- Pneumococcal vaccine
- Heamophilus influenza B vaccine
- Meningococcus vaccine
- Influenza vaccine pre- and yearly post-transplant
- Varcella vaccine if VZV antibody negative

- Hepatitis A vaccine if HAV antibody negative
- Hepatitis B vaccine (for HBsAg, HBcAb, HBsAb negative patients)

Pre-transplant assessments should include

- Baseline ophthalmology review to exclude active CMV retinitis
- Cervical and anal smears for HPV related CIN and AIN

7.0 Immunosuppressant Protocols

Early experience from the USA suggest higher than expected episodes of acute rejection in HIV positive renal transplant recipients [14]. Moreover, there are clinically important interactions between the calcineurin inhibitors (CNIs) and protease inhibitors (PIs) and the non-nucleoside reverse tranctriptase (NNRTI), Efavirenz [27]. Mycophenalate (MMF) may increase intracellular levels of abacavir, didanosine and tenofovir and could result in enhanced toxicity [27]. In the presence of PIs a major dose-reduction of CNIs may be required [28].

- Patients selected for transplant should have a trial of four weeks of CNI and MMF immune suppression with therapeutic drug monitoring pre-listing to determine the optimal dose of immune suppressants and PIs/NNRTIs on stable HAART.
- Once optimum doses have been decided, HAART therapy must not be changed without consultation with the transplant and HIV teams.
- Post-operation immune suppression will be according to local guidelines but should be at the level of a 'high risk' recipient and may include Basiliximab, a CNI, MMF and tapering glucocorticoids
- Polyclonal antibodies or OKT3 should not be used for induction or rescue
- Once started regular therapeutic drug monitoring will be required until stable drug levels have been achieved

7.1 Treatment of Acute Rejections

Episodes of acute graft rejection should be treated as per local guidelines. If acute rejection occurs, bolus therapy with high dose methylprednisolone needs to be used.

Current advice suggests that the treatment of two or more acute rejections is associated with a greatly increased complication rate. Under these circumstances consideration needs to be given to abandoning the graft. In view of the complexities of transplantation in HIV, all episodes of graft dysfunction should be assessed with a renal transplant biopsy if a diagnosis is not established following the usual work up to exclude extrarenal causes of graft dysfuntion

- Polyclonal antibodies or OKT3 should not be used for rescue in acute rejection.
- Bolus therapy with high-dose Methylprednisolone is the treatment of choice
- Consider graft nephrectomy after two or more episodes of acute rejection
- Consider all episodes of graft dysfunction for renal transplant biopsy

8.0 Monitoring of allograft function

In general, graft monitoring will follow local protocols.

- Kidneys with delayed graft function should be biopsied as soon as safe (and certainly within the first week) and weekly thereafter until function improved.
- Protocol biopsies are considered important in this complex setting and should be considered at 1 month, 3 months and 12 months.

9.0 Psychological support [29-32]

- In the pre-transplant assessment, ensure availability of counselling and provision of time for decision making and exploration of adaptation, coping and social support.
- Important issues that may need attention include: before and after body image, adherence with treatment, psychosexual difficulties and quality of life. (III)

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Appendix 1

INFORMED CONSENT

Kidney transplantation in HIV positive patients is still experimental although experience is growing. There is the risk that immunosuppression to prevent rejection of the transplant will encourage HIV growth and may increase the risk of tumours and infections. The drugs required to control HIV and to prevent transplant rejection have complex and sometimes unpredictable interactions.

In order for transplantation to be successful it will be necessary to administer a complex drug regime and to monitor all aspects of treatment and progress carefully. Extra blood tests, Xrays and scans will be required. Once discharged from hospital, out patient visits will be required 2-3 times a week for the first 3 months.

If transplant rejection is not easily controlled or if serious infections occur, the doctors looking after you may recommend removal of the transplanted kidney and return to dialysis.

In view of the complex nature of the treatment and uncertainties about drug interactions a transplant biopsy will be required on several occasions. At a minimum a biopsy will be performed at one month, 6 months and 12 months. It may be necessary at other times if kidney function deteriorates.

From the current literature it would appear that the success rate is about 80% at one year but the mortality rate may be as high as 5%. This has to be balanced by the risks and complications of long term dialysis.

Optional according to local guidelines - (In the event of a living donor, I agree to the donor being informed that I am HIV positive.)

I have read the above and agree to kidney transplantation:

SIGNED: (Patient) _____

SIGNED: (Witness) _____

DATE: _____