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The Voice of Transplantation in the UK

Kidney & Pancreas Transplantation in Patients With HIV

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1. INTRODUCTION

1.1 Scope and aim of the guidelines

Since the introduction of highly active antiretroviral therapy (HAART) in 1996, mortality in patients with human immunodeficiency virus (HIV) infection has decreased markedly. In parallel, morbidity from other chronic conditions such as kidney, liver and heart disease has increased. This is in part as a natural consequence of ageing, and in part due to the higher risk of solid organ failure in these individuals. This higher risk is a feature of the co-morbidities associated with HIV infection and with the metabolic consequences of anti-viral drug therapy.

Patients with HIV are at particular risk of the development of chronic kidney disease and, once established, end-stage kidney disease (ESRD) and dialysis substantially increase the risk of death and cardiovascular events in both the general and HIV-infected populations. Consequently, interest in organ transplantation in HIV-infected patients has increased and there has been a steady increase in both the number of transplants and the number of transplant centres serving this population.

These are the second guidelines on this subject published by the British Transplantation Society (BTS) and replace the earlier guidelines published in 2006 (1). These guidelines reflect the growing evidence base from published data on the several hundred carefully selected patients with HIV infection who have already received kidney and pancreas transplants. The aim is to provide a comprehensive summary of all aspects of assessment, selection and management of the HIV-positive transplant candidate. This document should be read in conjunction with existing guidelines regarding the management of non-HIV-infected kidney transplant recipients (2), but will focus on areas of special relevance to HIV-infected kidney and pancreas transplant recipients.

1.2 Process of writing and methodology

This document has been written under the auspices of the BTS Standards Committee. The guidance has been produced in line with the BTS Clinical Practice Guidelines and the recommendations of NHS Evidence (3). It has been produced with wide representation from UK clinicians involved in kidney transplantation and the management of HIV-infected patients.

A systematic review of the relevant literature and synthesis of the available evidence was undertaken by selected clinical experts. The editor, Dr Rachel Hilton, collated draft proposals and Dr Peter Andrews reviewed the text in his capacity as Chair of the Standards Committee of the BTS. The draft guidelines were placed on the BTS website in November 2014 for a period of open consultation, to which patient and transplant groups were encouraged to contribute. The final document was posted in January 2015.

Where available, these guidelines are based upon published evidence. With the exception of descriptive studies, the evidence and recommendations have been graded for strength. A small number of conference presentations have been included where relevant. The publication 'cut off' date for evidence was September 2014.

It is anticipated that these guidelines will next be revised in 2018.

1.3 Writing committee

Mr Martin Drage PhD FRCS
Consultant Transplant Surgeon, Guy's & St Thomas' NHS Foundation Trust

Dr Robert Elias MD MRCP
Consultant Nephrologist, King's College Hospital NHS Foundation Trust

Ms Esther Gathogo MPharm, MRPharmS
Clinical Pharmacist, Royal Free London & Department of Renal Sciences, King's College London

Dr Mark Harber PhD FRCP
Consultant Nephrologist and Honorary Senior Lecturer, Royal Free London NHS Foundation Trust

Dr Rachel Hilton PhD FRCP (Chair)
Consultant Nephrologist, Guy's & St Thomas' NHS Foundation Trust

Professor Saye Khoo MD MRCP
Professor of Clinical Pharmacology, University of Liverpool, and Honorary Consultant Physician in Infectious Diseases, Royal Liverpool & Broadgreen University Hospitals NHS Trust

Dr Frank Post MD PhD
Consultant Physician and Honorary Reader in HIV Medicine, King's College Hospital NHS Foundation Trust

1.4 Disclaimer

This document provides a guide to best practice, which inevitably evolves over time. All clinicians involved in this aspect of transplantation need to undertake clinical care on an individualised basis and keep up to date with changes in the practice of clinical medicine.

These guidelines represent the collective opinions of a number of experts in the field and do not have the force of law. They contain information/guidance for use by practitioners as a best practice tool at the time they were written. It follows that the guidelines should be interpreted in the spirit rather than to the letter of their contents. The opinions presented are subject to change and should not be used in isolation to define the management for any individual patient. The guidelines are not designed to be prescriptive, or to define a standard of care.

The British Transplantation Society (BTS) cannot attest to the accuracy, completeness or currency of the opinions contained herein and do not accept any responsibility or liability for any loss or damage caused to any practitioner or any third party as a result of any reliance being placed on the guidelines or as a result of any inaccurate or misleading opinion contained in the guidelines.

1.5 Declarations of interest

Editors, authors and contributors have worked to the standards detailed in the BTS Clinical Practice Guideline accessible at: http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current_Guidelines.aspx (3).

1.6 Grading of recommendations

In these guidelines, the GRADE system has been used to rate the strength of evidence and the strength of recommendations. This approach is consistent with that adopted by KDIGO in guidance relating to renal transplantation, and also with guidelines from the European Best Practice Committee, and from the Renal Association (2,4).

For each recommendation the quality of evidence has been graded as:

A (high)
B (moderate)
C (low)
D (very low)

For each recommendation, the strength of recommendation has been indicated as one of:

Level 1 (we recommend)
Level 2 (we suggest)
Not graded (where there is not enough evidence to allow formal grading)

These guidelines represent consensus opinion from experts in the field of transplantation in the United Kingdom. They represent a snapshot of the evidence available at the time of writing. It is recognised that recommendations are made even when the evidence is weak. It is felt that this is helpful to clinicians in daily practice and is similar to the approach adopted by KDIGO (2).

1.7 Definitions and abbreviations

The following definitions and abbreviations are used in this document:

AIN	Anal Intraepithelial Neoplasia
ALG	Anti-Lymphocyte Globulin
ART	Antiretroviral Therapy
ATG	Anti-Thymocyte Globulin
BHIVA	British HIV Association
BMI	Body Mass Index
cART	Combination Antiretroviral Therapy
CDC	Complement-Dependent Cytotoxicity
CIN	Cervical Intraepithelial Neoplasia

CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CsA	Ciclosporin
D:A:D	Data Collection on Adverse events of Anti-HIV Drugs
DTP	Diphtheria, Tetanus and Pertussis
eGFR	Estimated Glomerular Filtration Rate
EBV	Epstein Barr Virus
FCXM	Flow Cytometric Crossmatch
ESRD	End-stage Kidney Disease
HAART	Highly Active Antiretroviral Therapy
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHV	Human Herpesvirus
HIV	Human Immunodeficiency Virus
HIVAN	HIV-Associated Nephropathy
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
HTLV	Human T-cell Leukaemia Virus
IGRA	Interferon-Gamma Release Assays
IQR	Interquartile Range
IL-2RA	Interleukin-2 Receptor Antagonist
KDIGO	Kidney Disease: Improving Global Outcomes
KS	Kaposi Sarcoma
LTBI	Latent TB Infection
MAC	*Mycobacterium avium* Complex
MMR	Measles, Mumps and Rubella
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSM	Men who have Sex with Men
MTB	*Mycobacterium tuberculosis*
mTOR	Mammalian Target of Rapamycin
NNRTI	Non-Nucleoside-Reverse Transcriptase Inhibitors
NODAT	New Onset Diabetes After Transplantation
NTM	Non-tuberculosis Mycobacteria
PCP	Pneumocystis Pneumonia
PI	Protease Inhibitor

PML	Progressive Multifocal Leukoencephalopathy
PTLD	Post-Transplant Lymphoproliferative Disease
RR	Relative Risk
RRT	Renal Replacement Therapy
RSV	Respiratory Syncytial Virus
SPK	Simultaneous Pancreas and Kidney Transplantation
SrL	Sirolimus
Tac	Tacrolimus
TDM	Therapeutic Drug Monitoring
UK CHIC	UK Collaborative HIV Cohort Study
UNOS	United Network for Organ Sharing
VRE	Vancomycin-Resistant Enterococcus
VZV	Varicella Zoster Virus

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2. EXECUTIVE SUMMARY OF RECOMMENDATIONS

Indications for Kidney transplantation

We recommend that:

- All potential kidney transplant recipients are screened for HIV infection (1D)
- HIV per se is not a contraindication for kidney transplantation (1B)
- HIV-positive patients are wait-listed only if:
    a) They are concordant with treatment, particularly cART therapy (1D)
    b) Their CD4+ T cell counts are >100 cells/µL (ideally > 200 cells/ µL) and have been stable during the previous 3 months (1B)
    c) HIV RNA has been undetectable during the previous 6 months (1B)
    d) No opportunistic infections have occurred during the previous 6 months (1B)
    e) They have no history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma (1B)

We suggest that:

- The most appropriate anti-retroviral therapy is determined before transplantation in conjunction with an HIV specialist in order to anticipate potential drug interactions and appropriate dosing of medication (Not graded)

Indications for Pancreas Transplantation

We recommend that:

- Potential HIV positive pancreas transplant recipients are assessed by a centre with experience in kidney transplantation in HIV-positive patients, and also in solitary pancreas or islet transplantation (Not graded)

We suggest that:

- Diabetic patients in renal failure and with controlled HIV infection are considered for simultaneous kidney and pancreas transplantation (2D)
- Diabetic patients with severe hypoglycaemic unawareness may be considered for solitary pancreas or islet transplantation if they have well controlled HIV and kidney function that is stable and preserved (eGFR >40mL/min) (Not graded)

Contraindications to transplantation

We recommend that:

- The following are absolute contraindications to kidney transplantation in patients with HIV:
    a) Uncontrolled HIV infection (CD4+ T cell levels persistently <100 cells/μL during the last 6 months and HIV RNA persistently detectable during the last 3 months) (1C)
    b) Habitual and irremediable non-concordance, due for example to major psychiatric disease, irresolvable psychosocial problems or persistent substance abuse (1D)
    c) Multi-drug resistant HIV infection that cannot be controlled with currently available ART (1D)
    d) Positive complement-dependent cytotoxic (CDC) crossmatch (1D)
    e) Serious ongoing or recurring infection, including documented history of PML (1D)
    f) Active malignancy under treatment, metastatic cancer, disseminated or untreated cancer (1D)
    g) Pregnancy (1D)

We suggest that:

- The following are relative contraindications to kidney transplantation:
    a) Positive flow cytometric crossmatch (FCXM) (1D)
    b) Blood-type incompatibility (2D)
    c) Treated malignancy, including extracutaneous Kaposi sarcoma (2C)
    d) Severe and/or uncontrolled medical problems that are unlikely to improve after kidney transplantation and will shorten the patient's life expectancy (2D)
    e) Chronic liver disease (2D)
    f) Marked obesity (BMI >35 kg/m^2) (2D)
    g) HTLV infection (1D)

General assessment

We recommend that:

- Existing guidelines regarding evaluation, selection and preparation of the potential transplant recipient are followed for all potential transplant recipients with HIV disease (Not graded)
-

HIV-specific assessment

We recommend that:

- All transplant candidates undergo careful immuno-virological and antiretroviral status review. This includes CD4 cell count, HIV RNA level, current and prior antiretroviral therapies, HLA-B5701 status and HIV resistance profile (1D)
- Patients with HIV RNA levels <200 copies/mL may be considered suitable for solid organ transplantation if otherwise well and fully adherent with their medications (1C)
- Transplant candidates undergo serologic testing for syphilis, herpes simplex virus, Epstein-Barr virus, cytomegalovirus, varicella zoster virus, human T-cell leukaemia virus and *Toxoplasma gondii* (1D)
- Transplant candidates are tested for latent *Mycobacterium tuberculosis* infection with an interferon-gamma test with or without a concurrent Mantoux test following the testing strategy for immunocompromised patients in the current NICE Tuberculosis Guidelines (1C)
- Transplant candidates who test positive for latent *Mycobacterium tuberculosis* infection are assessed for any evidence of active tuberculosis disease (1C)
- Transplant candidates with evidence of active tuberculosis disease are treated according to current NICE guidance prior to transplantation (1C)
- Transplant candidates with latent *Mycobacterium tuberculosis* infection, in whom active disease has been excluded are treated for latent *Mycobacterium tuberculosis* infection, according to current NICE TB guidelines, prior to transplantation (1C)
- All transplant candidates are screened for viral hepatitis. Those found to be hepatitis B surface antigen or hepatitis C antibody positive should have their hepatitis B DNA / hepatitis C RNA levels quantified and be investigated for the presence of liver cirrhosis (1C)
- All hepatitis B surface antigen positive patients who are wait listed for solid organ transplantation receive treatment to ensure hepatitis B DNA is fully suppressed (1B)
- Patients considered for solid organ transplantation are assessed for the presence of cervical and/or anal neoplasia; those with advanced cervical/anal intraepithelial neoplasia (CIN/AIN III) or carcinoma in situ should receive treatment prior to transplantation (1D)

We recommend against:

- Kidney and/or pancreas transplantation in patients with liver cirrhosis (1B) and in those with evidence of active HCV replication (1C)

- Solid organ transplantation in patients with a history of Castleman's disease, human herpes virus 8 (HHV8)-related primary effusion lymphoma or Epstein-Barr virus (EBV)-related lymphoma (1D)

We suggest that:

- In selected cases, solid organ transplantation may be appropriate for patients with fully suppressed HIV RNA and a CD4 cell count below 200 cells/μL but above 100 cells/μL (2C)
- Antiretrovirals with nephrotoxic potential (specific tenofovir formulations and atazanavir) are avoided in the setting of kidney transplantation if suitable alternatives are available (Not graded)
- Antiretrovirals with significant drug-drug interactions with calcineurin inhibitors (ritonavir and cobicistat) are avoided in the setting of solid organ transplantation if suitable alternatives are available (2D)
- Transplant candidates from endemic regions are screened for *Strongyloides stercoralis* infection prior to transplantation (2D)
- Anti-HBc positive "alone" recipients (donor negative, recipient sAg and DNA negative) do not require routine antiviral prophylaxis against HBV reactivation, but this may be considered in those felt to be at increased risk of reactivation (e.g. those receiving lymphodepletion therapy) (2D)

<u>Pancreas-specific assessment</u>

We recommend that:

- Assessment of such potential transplant recipients is performed in a centre that regularly performs renal transplantation in HIV patients and that also regularly performs pancreas transplantation (1C)
- Transplant candidates are carefully counselled and informed that there is currently relatively little experience of pancreas transplantation performed in HIV-infected patients (Not graded)

We suggest that:

- Pancreas transplantation assessment in patients with HIV includes:
    a) Diabetic assessment (for hypoglycaemic unawareness, peripheral neuropathy, & autonomic neuropathy)

b) Vascular assessment (ultrasound assessment of leg vessels, and consider non-contrast CT of aorta and iliac arteries)
c) Consideration of a more extensive cardiac assessment (2C)

Pre-transplant immunisation

We recommend that:

- Hepatitis B virus (HBV) vaccine is administered to all non-immune patients (HBV surface antibody titres <10 mIU/mL) (1B)
- Hepatitis A virus (HAV) vaccine is administered to all non-immune patients (1D)
- Pneumococcal polysaccharide vaccine (PPV-23) is administered to all patients (1B)
- Varicella zoster vaccine (VZV) vaccine is administered to non-immune patients with CD4 cell counts >200 cells/µL (1C)
- Influenza vaccine is administered annually to patients awaiting solid organ transplantation (1B)

We suggest that:

- Diphtheria, tetanus and pertussis (DTP) vaccine is administered to all patients (2D)
- Measles, mumps and rubella (MMR) vaccine is administered to all patients who are non-immune to measles (2D)
- Human papilloma virus (HPV) vaccine is offered to patients at risk of HPV acquisition (2C)

Consideration of drug-drug interactions

We recommend:

- Continuation of antiretroviral therapy in the perioperative period following transplantation (1D)

We suggest:

- A full and current medication review as part of the assessment for solid organ transplantation, to be repeated at least twice yearly thereafter, and at every key therapeutic decision point (Not graded)
- A dose-finding trial of calcineurin-inhibitors prior to solid organ transplantation in order to determine optimum doses to initiate post-transplant (2D)

- Pre-emptive switching away from boosted protease-inhibitors (PI)-based antiretroviral regimens, if alternatives exist, in order to minimise drug interactions (2D)
- That all clinical correspondence carries a footer referring practitioners to the Liverpool HIV Drug Interactions Resource (www.hiv-druginteractions.org) (Not graded)

Induction and maintenance immunosuppression

We recommend that:

- All HIV-positive patients eligible for kidney transplantation are offered induction therapy at the time of transplantation (1C)
- For the majority of HIV-positive patients induction therapy is with an interleukin-2 receptor antagonist (IL-2RA) (1B)
- HIV-positive patients are given triple therapy maintenance immunosuppression started at the time of kidney transplantation, including steroids, a calcineurin inhibitor (CNI) and an anti-proliferative agent (1C)

We suggest that:

- Acute rejection is treated in HIV-positive kidney transplant recipients in the same way as HIV-negative kidney transplant recipients (2D)

Post-transplant prophylaxis

We recommend that:

- HIV-positive transplant recipients receive lifelong prophylaxis against *Pneumocystis* pneumonia following transplantation (1D)
- Prophylaxis against cytomegalovirus is indicated in CMV seronegative recipients of organs from CMV seropositive donors for a minimum of 3 months (1A)
- CMV seropositive transplant recipients receive either prophylaxis against CMV infection or PCR surveillance and pre-emptive therapy for a minimum of 3 months (1A)
- Transplant patients who are well and were not assessed and treated for *Mycobacterium tuberculosis* latent infection or disease before transplantation should be assessed as recommended for patients prior to transplantation (1C)
- Transplant patients who are well and were assessed and treated for *Mycobacterium tuberculosis* latent infection or disease before transplantation do not need re-assessment for *Mycobacterium tuberculosis* latent infection unless there is a new history of exposure to tuberculosis (1C)

- Transplant patients who are re-exposed to tuberculosis after transplantation should be assessed for *Mycobacterium tuberculosis* latent infection and/or disease as recommended in current NICE TB guidance on tuberculosis contact tracing (1C)

We suggest that:

- *Toxoplasma* IgG seropositive recipients with a $CD4^+$ count <200 cells/µL or any recipient of an organ from a donor seropositive for toxoplasmosis receive lifelong prophylaxis (2C)
- Where there is a reliable prior history of treated TB infection there is no need for further testing beyond symptom review and chest X-ray, and these individuals do not require TB prophylaxis unless TB re-exposure is suspected (2D)
- Prophylaxis against *Mycobacterium avium* complex (MAC) is indicated when the $CD4^+$ count is ≤ 50 cells/µL, and it be stopped when the CD4 count is >100 cells/µL for 6 months (2D)

<u>Monitoring allograft function</u>

We recommend that:

- Existing guidelines regarding post-operative care of the kidney transplant recipient are followed for all kidney transplant recipients with HIV disease (Not graded)

We suggest that:

- Local practice for monitoring of the pancreas allograft is followed (Not graded)

<u>Monitoring of HIV virological control</u>

We recommend that:

- Quantitative HIV RNA and CD4+ T-cell counts are measured regularly, with the first assays at 1 month after transplant and subsequent studies every 2-3 months for the first year then every 3-6 months thereafter (1B)
- If patients have persistent HIV viraemia, drug-resistance testing is carried out to determine treatment options (1D)

We suggest that:

- More frequent monitoring of CD4 count may be necessary in patients receiving depleting antibodies to determine the need for anti-infective prophylaxis (2D)

Choice of living versus deceased donor

We recommend that:

- Patients with HIV infection have the same access to living donor kidney transplantation as non-infected patients (1B)
- Patients with HIV infection are unsuitable to be living kidney donors (1D)

We suggest that:

- Potential donors for patients with HIV infection are informed of medical, surgical, and psychosocial factors that may heighten the recipient's morbidity and mortality risk but that disclosure of the recipient's HIV status is not mandatory (Not graded)

Consent and confidentiality

We recommend that:

- Existing guidelines on the ethics of deceased donor and living donor transplantation are followed for all transplantation involving people with HIV disease (Not graded)
- The standard of consent for HIV-positive transplant candidates is the same as for any other transplant (Not graded)
- Transplant teams must be satisfied that donor consent is adequate and that procedures for ensuring this are transparent and established in advance (Not graded)

We suggest that:

- Wherever possible, the recipient is encouraged to disclose their diagnosis of HIV to their donor (Not graded)
- All living donors are asked whether there are any medical conditions that would cause them to change their decision to donate, without highlighting HIV (Not graded)
- All living donors are made aware that there may be medical and social information about the recipient that is not disclosed (Not graded)
- All living donors are asked to acknowledge that they are aware that they will not be given confidential information about the recipient which is not deemed relevant to the outcome of the kidney transplant (Not graded)

Use of HIV-infected donors for HIV-infected recipients

We recommend that:

- Transplantation using organs from HIV-infected individuals is restricted to organs from deceased donors with:
    a) HIV viral load <50 copies/mL and CD4 count >200/µL for at least 6 months prior to brain injury
    b) Information about the donor virus such as historical genotype patterns where possible and current viral load
    c) No history of virological failure or drug resistance (1D)
- Recipients are counselled and give informed consent both at the time of listing and at the time of transplantation (1D)
- Patients with HIV-infection are unsuitable to be living kidney donors (1D)

We suggest that:

- HIV+ organ use is restricted to those centres that have experience in transplanting HIV+ patients (Not graded)

3. BACKGROUND

In 2013 108,000 people were living with HIV in the UK (1). The use of combination antiretroviral therapy (cART) has led to a dramatic reduction in opportunistic infections and death (2), and UK guidelines recommend that cART be provided to all patients with CD4 cell counts of less than 350 cells/µL (3). In 2011 almost 90% of those in need of treatment received cART, and 87% of those on cART achieved viral suppression (1). HIV-positive patients who start cART in accordance with current guidelines can expect a near-normal life expectancy (4). Unfortunately, 22% of patients in the UK remain unaware of their HIV diagnosis, and approximately half of those newly diagnosed with HIV infection present late (with AIDS or CD4 cell counts below 350 cells/µL) (1,5). The undiagnosed and late presenters, those that do not take up cART and those not virally suppressed remain at increased risk of opportunistic infections and death. Moreover, immunodeficiency is an important risk factor for chronic kidney disease (CKD) and end-stage kidney disease (ESRD) (6,7), and for liver disease progression in HCV-co-infected patients (8).

3.1 End-stage kidney disease and kidney transplantation in HIV positive patients

HIV-associated nephropathy (HIVAN) is the most severe form of CKD and the commonest cause of ESRD in HIV-positive patients in the UK (7). Patients of black ethnicity, who constitute one third of those diagnosed with HIV in the UK, are at increased risk of ESRD (7,9,10). Patients with HIVAN are typically young (mean age 36 years) with severe immune deficiency (median CD4 cell count 66 cells/µL) and advanced kidney failure (median estimated glomerular filtration rate [eGFR] 21 mL/min/1.73m^2) at diagnosis (11). Although suppression of HIV replication may improve or stabilise kidney function, the majority of patients progress to ESRD within 10 years of diagnosis of HIVAN (11-13).

In the US, HIV-positive African-American patients in Baltimore have been reported to start renal replacement therapy (RRT) at a rate of 1 per 100 person-years, with relatively poor outcomes (median survival 19.9 months) (13,14). By contrast, the incidence of ESRD among black HIV-positive patients attending seven UK HIV clinics was approximately six-fold lower (0.15 per 100 person-years) and survival following RRT initiation considerably better (85% at 5 years) (7). By 2007, an estimated 1% of black HIV-positive patients and 0.1% of those of other ethnicities in the UK had ESRD requiring renal replacement therapy (7).

The experience of kidney transplantation in HIV infection in the pre-cART era was disappointing, with a median patient survival of less than 4 years (16). However, the availability of cART has made it feasible to offer kidney transplantation to HIV-positive patients (15,16) and, by 2014, 85 patients in the UK had received a renal allograft (17). A meta-analysis of 12 case series comprising 254 patients who underwent kidney transplantation in the cART era reported one year patient survival of 93%, with acute graft rejection observed in 36% and infectious complications in 29% (18). Favorable graft survival rates (71-96% at two years, 83-100% at three years) have been reported in several recent case series (19-24). The largest prospective study to date included 150 HIV-positive patients and reported patient and graft survival rates of 88% and 74% at three years, which was somewhat below that of the general US kidney transplant population (25). Data from the UK Collaborative HIV Cohort Study (UK CHIC) suggest similar overall survival for HIV-positive kidney transplant recipients and those with wait-listed for kidney transplantation (85% vs. 89% at 5 years, respectively) (26).

Kidney transplantation in HIV-positive patients is complicated by a high rate of acute allograft rejection (range 15-70%) (15,16), with 33% of patients in the US series experiencing at least one rejection episode (25). Immunosuppression appears to be well tolerated, with few patients experiencing opportunistic infections, HIV disease progression or malignancy (15,16,27). The recent UK experience mirrors the above, with 3-year patient and allograft survival rates of 91.3% and 84.7% respectively and a cumulative incidence of acute allograft rejection of 48% at 12 months post-transplantation. Immunosuppression has been well tolerated and HIV viraemia uncommon, although renal complications are relatively frequent (17). Taken together, these studies suggest that kidney transplantation should be offered to HIV-positive patients with ESRD who are otherwise eligible.

3.2 Diabetes mellitus and pancreas transplantation

HIV infection is not associated with an increased risk of diabetes mellitus per se (28,29). The prevalence of diabetes mellitus in the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort was less than 3% at baseline. However, the use of cART has been associated both with the metabolic syndrome (30) and with diabetes mellitus (31). Some studies have suggested a class effect (protease inhibitors, non-nucleoside-reverse transcriptase inhibitors and nucleoside-reverse transcriptase inhibitors) (29,32) although, within these classes, individual drugs (indinavir, lopinavir/ritonavir, stavudine, zidovudine and

didanosine) may be associated with greater disturbances of glucose homeostasis (31,33,34).

Simultaneous pancreas and kidney transplantation (SPK) has been performed in a small number of HIV-positive patients, and at least one such operation has been performed in the UK (35). Grossi et al reported their experience in 4 patients: patient and kidney allograft survival was 100% after a median follow up of 45 months; one pancreatic graft was lost after 64 months; surgical complications and non-opportunistic infections were frequent (36). Although several case reports corroborate successful SPK transplantation, poor outcomes (early graft failure and death of the recipient) have also been reported (37).

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4. INDICATIONS FOR KIDNEY TRANSPLANTATION

Recommendations

We recommend that all potential kidney transplant recipients are screened for HIV infection (1D)

We recommend that HIV per se is not a contraindication for kidney transplantation (1B)

We recommend wait-listing HIV patients only if:

a) **They are concordant with treatment, particularly cART therapy (1D)**
b) **Their CD4+ T cell counts are >100 cells/μL (ideally >200 cells/μL) and have been stable during the previous 3 months (1B)**
c) **HIV RNA has been undetectable during the previous 6 months (1B)**
d) **No opportunistic infections have occurred during the previous 6 months (1B)**
e) **They have no history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma (1B)**

We suggest that the most appropriate anti-retroviral therapy is determined before transplantation in conjunction with an HIV specialist in order to anticipate potential drug interactions and appropriate dosing of medication (Not graded)

Rationale

Patients with HIV require specialised care in centres with appropriate expertise. Early reports of organ transplantation in HIV-infected people in the pre-cART era demonstrated poor outcomes. Screening for HIV infection should therefore be carried out in all potential kidney transplant recipients in order to identify those patients that will require specialised care.

Survival rates following kidney transplantation are higher in comparison with those of patients remaining on dialysis, demonstrating that kidney transplantation is a valid therapeutic option for HIV-positive patients with end-stage kidney disease (1). Based on the currently available data, HIV infection should not be considered a contraindication for transplantation, but should be considered along with other comorbidities in determining whether to proceed with transplantation and, if so, in determining appropriate

immunosuppression and adjunctive therapies.

Data on several hundred carefully selected HIV-positive patients show that patient and graft survival is similar to non-HIV patients at 1 and 3 years after transplantation (2-14). However, most of these studies applied stringent inclusion and exclusion criteria: a CD4+ count above 200 cells/μL of blood; an HIV-1 RNA viral load suppressed with treatment; and demonstrable concordance to a stable cART regimen for over 6 months. The selection criteria are similar in North America and Europe. Some (7,9,10,14), but not all (1,4,8,11), studies report disturbingly high acute rejection rates. There is high variability between studies, but in some series the rate is >50% (15). The explanation remains unclear, although immunological, pharmacological, and racial factors seem to have a role; in any case, the high rejection rate does not seem to significantly affect medium term allograft survival.

As to date these excellent results have been observed in highly selected patients, we recommend that the following criteria should be met:

- Patients demonstrate overall concordance with recommended treatment, and with cART therapy in particular
- CD4+ T cell levels are a minimum of 100 cells/μL and ideally >200 cells/μL and have been stable during the last 3 months (see section 8 for a more detailed explanation)
- HIV RNA has been undetectable during the last 3 months
- No opportunistic infections have occurred during the last 6 months
- No history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma

The reported higher rejection rate in some studies can potentially be attributed to the difficulty in obtaining a good balance between immunosuppression and controlled viral replication. Extremely complex management of calcineurin- and mTOR-inhibitors is recognized in patients on protease-inhibitor-based cART and to a lesser extent on NNRTI-based regimens (16). For these reasons, we suggest that the most appropriate anti-retroviral therapy for an individual patient should be discussed with the HIV/infectious disease team before transplantation. The use of anti-retrovirals such as integrase inhibitors that do not inhibit the P-450 system may simplify the use of immunosuppressants in this setting and decrease the frequency of rejection (17). There is however limited experience of the use of these agents in patients with ESKD, and there is potential for reduced absorption if co-prescribed with phosphate binders (18).

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5. INDICATIONS FOR PANCREAS TRANSPLANTATION

Recommendations

We suggest that diabetic patients in renal failure and with controlled HIV infection are considered for simultaneous kidney and pancreas transplantation (2D)

We suggest that diabetic patients with severe hypoglycaemic unawareness may be considered for solitary pancreas or islet transplantation if they have well controlled HIV and kidney function that is stable and preserved (eGFR >40mL/min) (Not graded)

We recommend that such patients are assessed by a centre with experience in kidney transplantation in HIV-positive patients and in solitary pancreas or islet transplantation (Not graded)

Rationale

It is increasingly regarded as routine practice to offer kidney transplantation to patients with kidney failure who have controlled HIV infection. In contrast, there is relatively little experience with simultaneous pancreas–kidney transplantation in HIV-positive patients with diabetes mellitus. Preliminary experience suggests that pancreas–kidney transplants can be performed using the same criteria as for kidney transplantation. However, there is a higher risk of procedure-related infectious complications (1-8).

Extrapolating the excellent results seen in carefully selected HIV-positive patients receiving kidney transplants, we therefore recommend that diabetic patients with kidney failure and controlled HIV infection may be considered for simultaneous kidney and pancreas transplantation.

In the general population, if a patient suffers from life-threatening hypoglycaemic unawareness in spite of best possible diabetic care, islet cell transplantation or solitary pancreas transplantation may be considered. To date there is no published experience of this type of transplantation in HIV-positive patients. However, extrapolating from experience in patients without HIV infection, it may be inferred that patients with severe hypoglycaemic unawareness may be considered for solitary pancreas or islet transplantation if they have

well controlled HIV and kidney function that is stable and well-preserved (eGFR >40mL/min). If transplantation is contemplated, we recommend that patients be assessed by a centre that regularly performs both solitary pancreas or islet transplantation and also kidney transplantation in HIV-positive patients. Careful counselling of the potential risks and benefits will be required, and such transplantation would ideally be undertaken in the context of a clinical trial.

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6. CONTRAINDICATIONS TO TRANSPLANTATION

Recommendations

We recommend that the following are absolute contraindications to kidney transplantation in patients with HIV:

a) **Uncontrolled HIV infection (CD4+ T cell levels persistently <200 cells/μL during the last 6 months and HIV RNA persistently detectable during the last 3 months) (1C)**
b) **Habitual and irremediable non-concordance, due for example to major psychiatric disease, irresolvable psychosocial problems or persistent substance abuse (1D)**
c) **Multi-drug resistant HIV infection that cannot be controlled with currently available ART (1D)**
d) **Positive complement-dependent cytotoxic (CDC) crossmatch (1D)**
e) **Serious ongoing or recurring infection, including documented history of PML (1D)**
f) **Active malignancy under treatment, metastatic cancer, disseminated or untreated cancer (1D)**
g) **Pregnancy (1D)**

We suggest that the following are relative contraindications to kidney transplantation:

a) **Positive flow cytometric crossmatch (FCXM) (1D)**
b) **Blood-type incompatibility (2D)**
c) **Treated malignancy, including extracutaneous Kaposi sarcoma (2C)**
d) **Severe and/or uncontrolled medical problems that are unlikely to improve after kidney transplantation and will shorten the patient's life expectancy (2D)**
e) **Chronic liver disease (2D)**
f) **Marked obesity (BMI >35 kg/m^2) (2D)**
g) **HTLV infection (1D)**

Rationale

The general criteria applicable to non-HIV kidney transplant waiting lists also apply. In addition, there are some criteria specific to patients with HIV.
Patients with low CD4 counts and/or persistently detectable HIV viraemia, patients with continued non-adherence to anti-retroviral therapy and patients with multi-drug resistant HIV infection are unlikely to benefit from transplantation (1).

The complement-dependent cytotoxicity (CDC) test employs lymphocyte targets to detect complement-fixing IgG and IgM antibodies and is positive when there are high levels of circulating antibodies specific for mismatched donor HLA antigens present at the time of transplantation. In most cases, the high risk of hyperacute rejection constitutes a contraindication to transplantation. For patients without HIV, some centres may advocate carefully planned pre-transplant desensitisation regimens together with close post-transplant immunological monitoring. There is no evidence to support the safety of such regimens in patients with HIV.

The flow cytometric crossmatch (FCXM) detects lower levels of anti-HLA antibodies and is not associated with an increased risk of hyperacute rejection but does predict early acute rejection and premature graft failure. Caution should be used when transplanting across a positive FCXM, especially if the T-cell (not just B-cell) crossmatch is positive or if the recipient has had a prior transplant.

Consideration may be given to a blood group-incompatible living donor kidney transplant when there are no other living kidney donors available although inclusion in the National Living Donor Kidney Sharing Scheme in order to achieve a blood group-compatible transplant may be preferable (2).

Infectious complications following solid-organ transplantation are common and may be life- or graft-threatening. Reactivation following immune suppression may occur with previously indolent infections, and therefore many of the infections listed below are considered contraindications to listing patients for solid organ transplantation (1):

- Deep and persistent infections or infections with resistant bacteria and fungi; for example empyema, *Aspergillus* infection and colonization, infection with other invasive fungi, and infection with Methicillin-resistant *Staphylococcus aureus* (MRSA) or Vancomycin-resistant *Enterococcus* (VRE)
- Untreated active chronic infections; for example active cytomegalovirus (CMV) and mycobacterial infection, unless there is clear evidence of successful treatment

- Progressive multifocal leukoencephalopathy (PML), which is a rare and usually fatal viral disease caused by a polyomavirus and occurs almost exclusively in people with severe immune deficiency. There is no known cure. Survival depends on adequate immune reconstitution which may be jeopardised by transplant immunosuppression
- Self-limiting infections within the last 30 days where there is a significant risk of re-activation with immunosuppressive therapy; for example, influenza or respiratory syncytial virus (RSV).

Solid organ transplant recipients are at high risk of occurrence of cancer including human papilloma virus-associated cervical and anal carcinoma. For treated solid-organ cancers, a variable period of recurrence-free survival is required before listing (3). Recommendations and advice may be obtained from the Israel Penn International Transplant Tumor Registry (http://ipittr.uc.edu). Consultation with an oncologist is required in most cases. In general, a two to five year waiting period is recommended after curative therapy for malignancy. This waiting period can be adjusted in individual cases dependent upon the estimated risk of recurrence, extent of disease at the time of treatment, type and grade of tumour, and the type of treatment given.

As cardiovascular disease is the main cause of mortality after transplantation, it is mandatory to detect and treat asymptomatic coronary artery disease, congestive cardiac failure resulting from valvular disease or cardiomyopathy, and constrictive pericarditis (4). Patients with advanced cardiopulmonary disease should be excluded.

Candidates with chronic hepatitis B or C or persistently abnormal liver function testing must have a hepatology evaluation prior to transplantation. Hepatitis B or C infection may be a contraindication to kidney transplantation, especially if there is evidence of active hepatitis or cirrhosis. Patients with quiescent disease and a benign liver biopsy can proceed to kidney transplantation, although treatment may be required in some (5).

Recipients with a body mass index over 35 kg/m^2 are at increased risk of complications after kidney transplantation, including surgical complications, longer length of stay, increased mortality, and higher risk of post transplant diabetes mellitus (6). The degree of obesity, and presence of intercurrent conditions such as age, cardiovascular disease and diabetes should be weighed in the decision to perform a transplant in an obese patient.

Since the human T-cell leukaemia virus (HTLV) is a risk factor for the development of leukaemia and myelopathy after transplantation, persons with HTLV must be informed of this

risk before surgery. Only those willing to accept this increased risk should be offered transplantation (7).

A remote history of treated tuberculosis does not contraindicate transplantation. In cases where the history suggests that there may be a persistent subclinical tuberculosis infection, a consultation with an infectious disease expert may assist in the decision to treat the recipient for tuberculosis, and whether it can be done before or after the transplant (8).

Multiple medical problems, which individually may not contraindicate transplantation, may produce an aggregate effect in a transplant candidate that would pose an unacceptable risk for transplantation. An example would be an elderly patient (over age 65), with serious cardiac disease, marked obesity, diabetes, or an extensive smoking history.

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7. GENERAL ASSESSMENT

Recommendation

We recommend that existing guidelines regarding evaluation, selection and preparation of the potential transplant recipient are followed for all potential transplant recipients with HIV disease (Not graded)

Rationale

Reports from both the United States and Europe have demonstrated favourable outcomes after kidney transplantation in the HIV-infected recipient (1,2), with early results demonstrating patient and graft survival rates that are comparable with HIV-negative kidney recipients. There is therefore no evidence that general assessment for transplant candidacy should be different for HIV-infected and non-HIV-infected kidney and pancreas transplant candidates. Current UK guidance was published by the Renal Association in 2011 (3). For HIV-specific aspects of pre-transplant assessment see section 8.

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8. HIV-SPECIFIC ASSESSMENT

Recommendations

We recommend that all transplant candidates undergo careful immuno-virological and antiretroviral status review. This includes CD4 cell count, HIV RNA level, current and prior antiretroviral therapies, HLA-B5701 status and HIV resistance profile (1D)

We suggest that in selected cases, solid organ transplantation may be appropriate for patients with fully suppressed HIV RNA and a CD4 cell count below 200 cells/μL but above 100 cells/μL (2C)

We recommend that patients with HIV RNA levels <200 copies/mL may be considered suitable for solid organ transplantation if otherwise well and fully adherent with their medications (1C)

We suggest that antiretrovirals with nephrotoxic potential (specific tenofovir formulations and atazanavir) are avoided in the setting of kidney transplantation if suitable alternatives are available (Not graded)

We suggest that antiretrovirals with significant drug-drug interactions with calcineurin inhibitors (ritonavir and cobicistat) are avoided in the setting of solid organ transplantation if suitable alternatives are available (2D)

We recommend that transplant candidates undergo serologic testing for syphilis, herpes simplex virus, Epstein-Barr virus, cytomegalovirus, varicella zoster virus, human T-cell leukaemia virus and *Toxoplasma gondii* (1D)

We recommend that transplant candidates are tested for latent *Mycobacterium tuberculosis* infection with an interferon-gamma test with or without a concurrent Mantoux test following the testing strategy for immunocompromised patients in the current NICE Tuberculosis Guidelines (1C)

We recommend that transplant candidates are tested for latent *Mycobacterium tuberculosis* infection following the testing strategy for immunocompromised HIV infected patients in the current NICE Tuberculosis Guidelines (1C)

We recommend that transplant candidates who test positive for latent *Mycobacterium tuberculosis* infection are assessed for any evidence of active tuberculosis disease (1C)

We recommend that transplant candidates with evidence of active tuberculosis disease are treated according to current NICE guidance prior to transplantation (1C)

We recommend that transplant candidates with latent *Mycobacterium tuberculosis* infection, in whom active disease has been excluded are treated for latent *Mycobacterium tuberculosis* infection, according to current NICE TB guidelines, prior to transplantation (1C)

We suggest that transplant candidates from endemic regions are screened for *Strongyloides stercoralis* infection prior to transplantation (2D)

We recommend that all transplant candidates are screened for viral hepatitis. Those found to be hepatitis B surface antigen or hepatitis C antibody positive should have their hepatitis B DNA / hepatitis C RNA levels quantified and undergo investigation for the presence of liver cirrhosis (1C)

We recommend that all hepatitis B surface antigen positive patients who are wait listed for solid organ transplantation receive treatment to ensure hepatitis B DNA is fully suppressed (1B)

We suggest that anti-HBc positive "alone" recipients (donor negative, recipient sAg and DNA negative) do not require routine antiviral prophylaxis against HBV reactivation, but this may be considered in those felt to be at increased risk of reactivation (e.g. those receiving lymphodepletion therapy) (2D)

We recommend against kidney and/or pancreas transplantation in patients with liver cirrhosis (1B) and in those with evidence of active HCV replication (1C)

We recommend that patients considered for solid organ transplantation are assessed for the presence of cervical and/or anal neoplasia; those with advanced cervical/anal intraepithelial neoplasia (CIN/AIN III) or carcinoma in situ should receive treatment prior to transplantation (1D)

We recommend against solid organ transplantation in patients with a history of extra-cutaneous Kaposi sarcoma, Castleman's disease, human herpes virus 8 (HHV8)-related primary effusion lymphoma or Epstein-Barr virus (EBV)-related lymphoma (1D)

Rationale

In addition to the general objectives of pre-transplant assessment (see section 6), there are additional objectives from an HIV perspective. These are:

a) To ensure infectious complications post-transplantation are minimised through screening, immunisation and/or the provision of treatment; and

b) To formulate a management plan that allows the safe co-administration of combination antiretroviral therapy (cART) and immunosuppression.

8.1 CD4 cell count, HIV RNA and antiretroviral therapy

The 2005 BTS guidelines proposed that HIV-positive patients who are considered for kidney transplantation should have CD4 cell counts above 200 cells/μL, undetectable HIV RNA levels, and future antiretroviral options (1). The median CD4 cell count in the National Institutes of Health funded United States multicentre prospective trial was 524 (IQR 385-672) and in the UK cohort study of kidney transplantation in HIV-positive patients 366 (278-495) cells/μL (2,3). For liver transplantation, a CD4 cell count criterion above 100 cells/μL has been applied as many patients have splenomegaly-induced reductions in CD4 T-cell counts (4).

Applying these criteria, the incidence of opportunistic infection in kidney transplant recipients has proved to be low (2,3). It is unclear whether patients with CD4 cell counts below 200 cells/μL but with fully suppressed HIV RNA levels are at greater risk of infectious complications post-transplantation. The majority of patients in the UK cohort study had a history of very advanced immunodeficiency (median CD4 cell nadir 78, IQR 39-105 cells/μL), and four patients received renal allografts with CD4 cell counts below 200 (median 98, range 76-194) cells/μL; none of these patients experienced opportunistic infections or HIV disease progression (3). It thus appears that, in carefully selected cases, solid organ transplantation may also be an option for patients with fully suppressed HIV RNA and an absolute CD4 cell count below 200 cells/μL, particularly where the relative CD4 count is ≥13%. Where cART

has only recently been started clinicians are encouraged to wait for CD4 counts to rise before listing for transplantation.

Whereas a fully suppressed HIV RNA level (<50 copies/mL) remains desirable, low-level viraemia is commonly encountered in HIV-positive patients on stable combination antiretroviral therapy (cART). There is no evidence that low level viraemia adversely affects clinical outcomes or allograft function in solid organ transplantation. Consequently, patients with HIV RNA levels <200 copies/mL may be considered suitable for solid organ transplantation if otherwise well and fully adherent to their medication. For such patients a sensitive ARV resistance test (e.g. using nested PCR) may be considered.

The appropriate cART regimen for patients awaiting solid organ transplantation is determined by the presence of HIV resistance mutations and the recipient's ability to tolerate specific antiretrovirals. Current guidelines recommend that thymidine analogues (stavudine and zidovudine) and didanosine are avoided (5). Non-nucleoside reverse transcriptase and integrase inhibitors offer the advantage of minimal or no drug-drug interactions with immunosuppressants, while ritonavir- (or cobicistat-) boosted protease or integrase inhibitors require careful adjustment of especially calcineurin-inhibitors (see section 10). Of the commonly used antiretrovirals, tenofovir disoproxil fumarate and atazanavir have been associated with kidney injury and kidney disease progression, and these drugs are ideally avoided in the setting of kidney disease and kidney transplantation (5,6).

8.2 Screening for latent infections

It is important to know whether potential transplant recipients have had exposure to the common herpes viruses: herpes simplex virus (HSV); Epstein-Barr virus (EBV); cytomegalovirus (CMV); and varicella zoster virus (VZV).

HSV and VZV negative recipients may develop severe primary HSV/VZV infection if exposed post-transplantation. EBV sero-negative recipients of an organ from an EBV seropositive transplant have a seven-fold increased risk of post-transplant lymphoproliferative disorder (PTLD) (7). Knowledge of recipient CMV serology at transplantation is essential to guide antiviral prophylactic strategies (8). Immunisation should be offered to all VZV IgG negative patients with CD4 cell counts >200 cells/µL (9).

HTLV-I was listed as a contraindication to kidney transplantation in HIV positive patients in the 2005 BTS guidelines (1). Although cases of HTLV-1-associated myelopathy or adult T-cell leukaemia have been reported, the incidence of these complications is unknown. Case series from Japan and Iran have reported no cases of myelopathy or leukaemia among 31 HTLV-1-infected kidney transplant recipients who were mostly managed with current immunosuppression regimens (10-12). Specialist advice should be sought before wait listing HTLV-1 positive transplant candidates.

Toxoplasma negative recipients have a fifteen-fold increased risk of post-transplant toxoplasmosis (13); knowledge of recipient toxoplasma serology at transplantation may be useful to guide prophylactic strategies (see section 12).

Solid organ transplant recipients are at increased risk of developing tuberculosis (TB) (14,15). TB post-transplantation is a serious complication; the diagnosis of TB is challenging and its treatment complex in patients on antiretroviral and immunosuppressive therapy. In areas of low rates of *Mycobacterium tuberculosis* (MTB) transmission, most cases of TB arise from reactivation of latent TB infection (LTBI); LTBI should be actively sought and treated prior to solid organ transplantation. LTBI can be diagnosed through the detection of MTB-specific immune responses (interferon-gamma release assays [IGRAs] and tuberculin skin tests) in people with no prior history of TB disease. IGRAs are considered to be more sensitive and specific than tuberculin skin tests to detect LTBI, especially in immunocompromised patients (16). The use of IGRAs is further supported by a study that associated a positive IGRA with incident TB in kidney transplant recipients (17). There are no data to suggest that patients who have received a full course of rifamycin-based treatment for active TB are at greater risk of recurrent TB post-transplantation; LTBI testing is unhelpful in these patients and chemoprophylaxis is not indicated unless a there is a history of TB re-exposure following the completion of previous TB treatment. Examples of exposure to TB include receipt of an organ from a donor who was infected with Mycobacterium tuberculosis or contact with a case of infectious tuberculosis.

In endemic areas and also in non-endemic areas where there is a large immigrant population, screening for *Strongyloides stercoralis* may be considered in order to allow provision of ivermectin to those with positive serology to prevent hyperinfestation syndrome post-transplantation (18,19).

8.3 Viral hepatitis

The prevalence of hepatitis B (HBV) and hepatitis C (HCV) is increased in HIV-positive patients (20). High rates of liver disease progression (cirrhosis, hepatocellular carcinoma) have been reported in untreated HBV co-infected patients who underwent kidney transplantation (21). With the advent of oral anti-HBV agents, improved outcomes have been reported for HBV-infected kidney transplant recipients (22,23). It follows that HIV-positive patients with replicating HBV co-infection who are listed for kidney and/or pancreas transplantation would ideally be treated with nucleoside or nucleotide analogues (lamivudine/emtricitabine, entecavir and tenofovir) as part of, or additional to the HAART regimen to render them aviraemic prior to and after transplantation.

The prevalence of the isolated hepatitis B core Ab phenotype (hepatitis B surface antigen negative hepatitis B surface antibody negative, and hepatitis B core antibody positive) is particularly high among HIV-positive patients. Controversy exists regarding both the significance of this phenotype and the risk of progressive liver disease, as well as the need for hepatitis B vaccination in this population (24). Routine antiviral prophylaxis is not recommended for such isolated anti-HBc positive recipients but may be considered in those felt to be at increased risk of reactivation (e.g. lymphodepletion therapy) (25)

Regarding HCV co-infection, there is controversy about the risk of liver disease progression with immunosuppression and the development of HCV transplant glomerulopathy (26-28), with one study demonstrating severe evolution of HCV liver disease in kidney recipients (26). In contrast, a 10-year study that followed 51 HCV-positive kidney transplant recipients with serial liver biopsies showed that HCV infection was not harmful on liver histology in at least 50% of patients (27), and another study showed stable disease or regression of liver fibrosis in 77% of patients after kidney transplantation (28). Among HIV-positive kidney transplant recipients, somewhat higher early mortality has been observed for those co-infected with HCV (11.7% vs. 3.9% at 1 year, p=0.09) (2). We thus recommend that kidney and/or pancreas transplant candidates are treated for HCV prior to transplantation.

8.4 Malignancy (see also section 6)

The incidence of human papilloma virus (HPV)-associated cancer is markedly increased in both HIV-positive patients and kidney transplant recipients (29). HIV-positive women should have annual cervical smears performed (30). In women with abnormal smears, colposcopy should be performed to exclude intra-epithelial neoplasia. The role of anal cytology and high

resolution anoscopy as a screening tool for the early detection of anal cancer in men who have sex with men (MSM) remains to be defined; the assessment of HIV-positive MSM should include an enquiry of anal symptoms and a digital rectal examination (30).

The incidence of Kaposi sarcoma (KS) is increased in HIV-positive patients and kidney transplant recipients (29). KS was an infrequent complication in the US and UK HIV/kidney transplant series (3 of 185 patients), and all cases of KS were restricted to the skin (2,3).

Castleman's disease and primary effusion lymphoma, conditions that are caused - like KS - by human herpes virus 8 (HHV8), have been reported in HIV-positive liver transplant recipients; a history of these tumours is a contraindication to solid organ transplantation (2).

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9. PANCREAS-SPECIFIC ASSESSMENT

Recommendations

We suggest that pancreas transplantation assessment in patients with HIV includes:

- **Diabetic assessment (for hypoglycaemic unawareness, peripheral neuropathy, & autonomic neuropathy)**
- **Vascular assessment (ultrasound assessment of leg vessels, and consider non-contrast CT of aorta and iliac arteries)**
- **Consideration of a more extensive cardiac assessment (2C)**

We recommend that assessment of these patients is performed in a centre that regularly performs renal transplantation in HIV patients and that also regularly performs pancreas transplantation (1C)

We recommend that the transplant candidate is carefully counselled and informed that there is currently relatively little experience of pancreas transplantation in HIV-infected patients (Not graded)

Rationale

The emphasis of the evaluation is to identify and treat all coexisting medical problems that may increase the morbidity and mortality of the surgical procedure and adversely impact the post-transplantation course. In addition to a thorough medical evaluation, the social issues of the patient should be evaluated to determine conditions that may jeopardize the outcome of transplantation, such as financial and travel restraints or a pattern of non-concordance.

In addition to the general and HIV-specific assessments detailed in sections 7 and 8, patients being assessed for pancreas transplantation should ideally also be assessed for the presence of hypoglycaemic unawareness, peripheral neuropathy, and autonomic neuropathy. Where these conditions or suggestive symptoms are present a more formal review led by a diabetes specialist must be sought. A C-peptide level must be measured to determine whether the transplant candidate has type I or type II diabetes.

Most patients will require a more extensive vascular assessment to include ultrasound assessment of leg vessels, and possibly non-contrast CT assessment of the aorta and iliac arteries.

A complete cardiac workup, including angiography, may not be necessary in every patient. However, individuals aged 50 years or over, or with significant cardiac history, type I diabetes, or end-stage kidney disease for more than 3 years must undergo a complete evaluation to rule out significant coronary artery disease. This would include a 12-lead ECG and dynamic cardiac assessment (exercise/dipyridamole myocardial perfusion scan or dobutamine stress echocardiography), leading to coronary angiography where indicated.

10. PRE-TRANSPLANT IMMUNISATION

Recommendations

As part of the work-up for solid organ transplantation we recommend that:

- **Hepatitis B virus (HBV) vaccine is administered to all non-immune patients (HBV surface antibody titres <10 mIU/mL) (1B)**
- **Hepatitis A virus (HAV) vaccine is administered to all non-immune patients (1D)**
- **Pneumococcal polysaccharide vaccine (PPV-23) is administered to all patients (1B)**
- **Varicella zoster vaccine (VZV) vaccine is administered to non-immune patients with CD4 cell counts >200 cells/μL (1C)**

We suggest that:

- **Diphtheria, tetanus and pertussis (DTP) vaccine is administered to all patients (2D)**
- **Measles, mumps and rubella (MMR) vaccine is administered to all patients who are non-immune to measles (2D)**
- **Human papilloma virus (HPV) vaccine is offered to patients at risk of HPV acquisition (2C)**

We recommend that influenza vaccine is administered annually to patients awaiting solid organ transplantation (1B)

Rationale

10.1 Hepatitis B virus (HBV)

HIV-positive patients are at increased risk of acquiring HBV infection and for such infections to become chronic. Chronic HBV infection is present in 6-10% of HIV-positive persons in the UK and co-infected persons are at increased risk of progression to cirrhosis and liver cancer, and approximately 10-fold higher risk of death (1,2). Solid organ transplantation is an additional risk factor for more severe, more persistent, and more rapidly progressive HBV infection (3). HBV vaccination significantly reduces the risk of incident HBV infection in HIV-positive persons (4). The British HIV Association (BHIVA) and the UK Renal Association

recommend HBV vaccination for all non-immune patients (5,6). The use of larger or more frequent HBV vaccine doses may result in better response rates (7,8).

10.2 Hepatitis A virus (HAV)

Patients with chronic liver disease are at risk of severe and fulminant hepatitis A, and BHIVA recommends immunisation of those at risk of HAV infection (5). HAV vaccine is safe and well tolerated in HIV-infected patients (5) and those with end-stage kidney disease (9). BHIVA guidelines suggest that the standard vaccination schedule (two doses at 0 and 6-12 months) is administered to those with CD4 cell counts >300 cells/µL, and that those with CD4 cell counts <300 cells/µL should receive three doses over 6-12 months (5).

10.3 Pneumococcus

Solid organ transplant recipients and HIV positive patients are at increased risk of invasive pneumococcal disease, and pneumococcal infections may cause significant morbidity and mortality (10,11). BHIVA guidelines recommend pneumococcal vaccination for all HIV-positive patients with CD4 cell counts >200 cells/µL, and for those with CD4 cell counts <200 cells/µL if there are additional risk factors such as chronic kidney and liver disease or diabetes mellitus, unless pneumococcal vaccine has been administered in the last 3 years (5). Vaccination should be repeated every 3-5 years.

10.4 Varicella-Zoster virus (VZV)

Patients with HIV infection and solid organ transplant recipients are at risk of developing severe illness from either primary or reactivation disease with VZV. Primary varicella infection may be complicated by severe or disseminated cutaneous disease, secondary bacterial infection of skin lesions, and visceral dissemination with pneumonitis and disseminated intravascular coagulation. HIV-positive persons and solid organ transplant recipients have a higher frequency of zoster than the general population. Although most have an uncomplicated clinical course, these patients are more prone to complications including multi-dermatomal, disseminated and chronic atypical skin rashes. Acute retinal necrosis and neurological syndromes including encephalitis, myelitis and meningitis can occur in the absence of rash.

BHIVA guidelines recommend VZV vaccination for asymptomatic, VZV IgG seronegative HIV positive adults with a CD4 cell count >400 cells/µL and suggest that vaccination may also be considered for patients with CD4 counts of 200-400 cells/µL who are stable on cART (5). The UK Renal Association also recommends immunisation of VZV IgG seronegative patients before transplantation (6).

10.5 Diphtheria, tetanus and pertussis (DTP)

Diphtheria, tetanus and pertussis vaccine is safe and BHIVA recommends vaccination for all HIV-positive persons in accordance with standard recommendations (5). As most patients will have been previously vaccinated, we suggest a booster is administered to those in whom the vaccine was last administered >10 years ago.

10.6 Measles, mumps and rubella (MMR)

BHIVA guidelines recommend that HIV-positive persons be screened for measles IgG and offered MMR vaccine if they are measles IgG seronegative and asymptomatic with a CD4 count >200 cells/µL (5). Two doses of MMR vaccine must be given, with the second dose given at least one month after the first (5).

10.7 Human papilloma virus (HPV)

HIV-positive patients and solid organ transplant recipients with ano-genital HPV infection are at substantially increased risk of developing cervical and ano-genital cancers (12). While vaccination is best completed before subjects become sexually active, recent data suggest that 46-53% of 16-23 year old HIV-positive women and unselected HIV-positive men who have sex with men may be negative for the high-risk HPV types 16 and 18 (13,14). These data suggest that vaccination of selected, sexually experienced HIV-positive young adults may be beneficial in terms of reducing the risk of high risk HPV acquisition, and thus in terms of developing cervical or ano-genital cancer.

10.8 Influenza

Influenza vaccines are recommended for people with serious medical conditions including HIV infection and solid organ transplantation. BHIVA guidelines recommend influenza vaccination for all HIV-positive patients, especially if additional risk factors such as chronic kidney and liver disease or diabetes mellitus are present (5). Vaccination is recommended annually.

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11. CONSIDERATION OF DRUG-DRUG INTERACTIONS

Recommendations

We suggest a full and current medication review as part of the assessment for solid organ transplantation, to be repeated at least twice yearly thereafter, and at every key therapeutic decision point (Not graded)

We suggest a dose-finding trial of calcineurin-inhibitors prior to solid organ transplantation in order to determine optimum doses to initiate post-transplant (2D)

We suggest pre-emptive switching away from boosted protease-inhibitors (PI)-based antiretroviral regimens, if alternatives exist, in order to minimise drug interactions (2D)

We recommend continuation of antiretroviral therapy in the perioperative period following transplantation (1D)

We suggest that all clinical correspondence carries a footer referring practitioners to the Liverpool HIV Drug Interactions Resource (www.hiv-druginteractions.org) (Not graded)

Rationale

From a pharmacy perspective, the general objectives for the preparation for solid-organ transplantation are:

a) to ensure that all medicines are reviewed prior to transplantation for potential drug-drug interactions
b) to ensure that the recipient receives optimal doses of calcineurin inhibitors (CNI) to reduce the risk of graft rejection

Drug errors are common, affecting at least 1 in 10 prescribed medicines (1,2). Harm may result, particularly in patients with pre-existing liver or kidney impairment, with multiple co-morbidities, and those receiving multiple medications.

The first step in preventing harm, and in recognising medication error when it occurs, is to ensure current and complete medication recording. This is especially important in HIV-positive patients with end-stage kidney or liver disease who are typically on multiple medications to manage their chronic conditions. The aim of medicines reconciliation is to ensure accurate and up-to-date documentation of all prescribed (and non-prescribed) medicines at the time of transplantation and to predict potential interactions between these and the intended immunosuppressants (3). Furthermore, it provides an opportunity to assess adherence, to document a stable cART regimen for ≥6 months as part of the HIV-specific inclusion criteria for solid organ transplantation, and to assess future antiretroviral treatment options. The medication review during transplant work-up need to be verified with carers, with the GP, and across all relevant teams, and must encompass all medications including antivirals, anti-hypertensives, medicines used in conjunction with renal replacement therapy, herbal remedies, vitamins, over-the-counter products and any other medication.

Immunosuppressant drugs and antiretroviral drugs (most notably protease-inhibitors [PIs] and non-nucleoside reverse transcriptase-inhibitors [NNRTIs]) have the potential to interact as they are handled by similar drug transporters (p-glycoprotein [P-gp]) and gastrointestinal and hepatic metabolic [cytochrome (CYP) P450 enzymes] pathways (4). Protease-inhibitors, particularly when boosted by ritonavir, are potent P-gp transporter and CYP enzyme inhibitors that dramatically increase CNI and mammalian target of rapamycin (mTOR)-inhibitor exposure, thus requiring significant dose reductions e.g. 90% ciclosporin and 99% tacrolimus dose reduction; NNRTIs by contrast are enzyme-inducers that reduce CNI and mTOR-inhibitor drug concentrations, although the latter require minimal dose increment (4). No significant drug interactions have been noted for CNIs or mTOR-inhibitors when co-administered with the integrase-inhibitor, raltegravir, and potentially with dolutegravir (4). Table 1 summarises the potential drug interactions for commonly used antiretrovirals.

To optimise CNI concentrations following transplantation and help manage the drug-drug interactions between immunosuppressant drugs and ART, a dose-finding trial of CNI immunosuppression with therapeutic drug monitoring may be considered as part of the work-up for solid organ transplantation, and is recommended in patients whose cART contains protease-inhibitors (see section 8). The choice of CNI is dependent on local transplant protocols, although patient concordance may be endangered by complicated dosing schedules that may require, for example, intake of 0.5 mg tacrolimus every 8-10 days. The duration of the trial is dependent on achieving steady-state therapeutic whole blood trough concentrations (e.g. 3 consecutive measurements within the target range). Table 2

summarises the CNI doses and drug concentrations that were observed in the first 2 months post-kidney transplantation in 31 patients in the UK (5).

During the perioperative period, in case of swallowing difficulties, the Liverpool Guidance on "Antiretroviral Dosage Forms for Swallowing Difficulties" offers alternative antiretroviral drug formulations or administration guidance (6).

It is critical that both clinicians and patients are aware of the implications of the drug interactions between cART and immunosuppressants, and that the timing of doses and immunosuppressant concentrations, as well as drug dosages and frequencies, are properly communicated and documented.

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Table 1 Antiretroviral-immunosuppressant drug interactions for selected antiretrovirals

Antiretroviral Class	Ciclosporin	Tacrolimus	Sirolimus
Ritonavir-boosted Protease-Inhibitors (PI): Atazanavir; Darunavir; Lopinavir/ritonavir (Kaletra)	CsA exposure increased requiring a dose reduction e.g. CsA 20-50 mg/day. TDM for dose optimisation	Tac exposure increased requiring dose reduction e.g. 0.5 mg once every 5-14 days. TDM for dose optimisation	SrL exposure increased requiring dose reduction e.g. 1-2 mg once a week. TDM for dose optimisation
Nucleotide/Nucleoside Reverse Transcriptase-Inhibitors (NRTI): Tenofovir; Abacavir; Zidovudine; Emtricitabine; Lamivudine	No anticipated effect on CsA exposure	No anticipated effect on Tac exposure. Possible small increase in Tac C_{max} with tenofovir	No anticipated effect on SrL exposure
Non-Nucleoside Reverse Transcriptase-Inhibitors (NNRTI): Efavirenz; Nevirapine; Etravirine	CsA exposure decreased requiring slight dose increase. TDM for dose optimisation	Tac exposure decreased requiring slight dose increase. TDM for dose optimisation	SrL exposure decreased requiring slight dose increase. TDM for dose optimisation
Rilpivirine	No clinically significant interaction expected. Possible small increase in rilpivirine concentration.	No clinically significant interaction expected. Possible small increase in rilpivirine concentration	No clinically significant interaction expected

Integrase-Inhibitors: Raltegravir; Dolutegravir (not licensed)	No anticipated effect on CsA exposure	No anticipated effect on Tac exposure	No anticipated effect on SrL exposure
CCR5 Antagonist: Maraviroc	No anticipated effect on CsA exposure. CsA could potentially increase maraviroc concentrations	No anticipated effect on Tac exposure	No anticipated effect on SrL exposure

For further information see: http://www.hiv-druginteractions.org; http://hep-druginteractions.org

Abbreviations: CsA ciclosporin; Tac tacrolimus; SrL sirolimus; TDM therapeutic drug monitoring

Table 2 Example of median [IQR] tacrolimus (Tac) and ciclosporin (CSA) doses and whole blood trough concentrations from 31 HIV positive kidney transplant recipients during the first 2 months post-transplantation (ref. 5)

	N	Tac dose	Tac concentration (ng/mL)	CsA dose	CsA concentration (ng/mL)
Protease-inhibitors (PIs)	14	0.8 [0.3, 4] mg/week	10 [5,23]	30 [25,50] mg/day	279 [218,363]
Non-nucleoside reverse transcriptase-inhibitors (NNRTIs)	17	16 [10-20] mg/day	8 [6,11]	775 [550,900]	245 [183,319]

Please note:

(1) Tacrolimus is dosed weekly when co-administered with ritonavir-boosted PI

(2) The wide inter-quartile range of the doses used

12. INDUCTION AND MAINTENANCE IMMUNOSUPPRESSION

Recommendations

We recommend that all HIV-positive patients eligible for kidney transplantation are offered induction therapy at the time of transplantation (1C)

We recommend that for the majority of HIV-positive patients induction therapy is with an interleukin-2 receptor antagonist (IL-2RA) (1B)

We recommend that HIV-positive patients are given triple therapy maintenance immunosuppression started at the time of kidney transplantation, including steroids, a calcineurin inhibitor (CNI) and an anti-proliferative agent (1C)

We suggest that acute rejection is treated in HIV-positive kidney transplant recipients in the same way as HIV-negative kidney transplant recipients (2D)

Rationale

As the experience of transplanting patients with HIV has grown, initial fears that immunosuppression would exacerbate immunodeficiency have proved unfounded. Infection and cancer rates seem largely similar to those from HIV-negative transplant recipients and there appears to be no significant progression of HIV infection. Any viraemia that does occur post-transplant appears to be almost exclusively due to stopping or reduction (intentional or otherwise) of cART. However, and somewhat counter-intuitively, rejection rates consistently appear to be 2 to 3 times higher than that of HIV-negative kidney transplant recipients. The cause of the high incidence of acute rejection is unclear but the impact is significant; the HIV-TR Investigators study found that acute rejection had a hazard ratio of 2.8 for graft loss (1). On the basis of these data it seems that conventional immunosuppression is appropriate for HIV-positive kidney transplant recipients and, indeed, that such patients are at higher immunological risk.

12.1 Induction agents

In HIV-negative kidney transplantation, IL-2 receptor antagonists (IL-2RA) have been shown to be superior to placebo. A recent Cochrane review showed reduced acute rejection (RR 0.77) and death-censored graft survival rates (RR 0.74) with no increment in infectious or malignant complications (2). There are insufficient data comparing IL-2RA with placebo in HIV-positive recipients but, given the immunological effect of these agents, it seems reasonable to extrapolate that their use is appropriate in this group, particularly given the higher rate of acute rejection.

The evidence base for the benefit of induction with lymphocyte-depleting agents in kidney transplantation is less comprehensive than that for IL-2RA. However, in the general population, lymphocyte-depleting agents are associated with lower acute rejection rates and reduced graft loss compared with placebo. The benefits of lymphocyte-depleting agents are most significant in terms of graft survival in high immunological risk patients with high levels of anti-HLA antibodies.

Lymphocyte-depleting antibodies (ATG, ALG and OKT3) are all associated with significant increased infectious and malignant complications in non-HIV kidney transplants. For this reason, the previous BHIVA guidelines on transplantation in HIV-positive patients did not recommend their use either for induction or the treatment of acute rejection (3). Since then, however, there have been reports of the successful and safe use of ATG in HIV-positive patients although in the HIV-TR Investigators study, the 32% of patients receiving ATG induction experienced a small increase in death and graft loss (RR 2.1) compared with non-ATG induction (1). However, it is not clear why ATG was chosen in these patients and whether they were at higher immunological risk in comparison with patients not receiving depleting antibodies. A more recent analysis of the scientific registry of transplant recipient data in the USA from 2003–11, including 516 HIV positive kidney transplant recipients, found a 61% reduction in acute rejection at one year in HIV-positive kidney transplant recipients who received ATG induction in comparison with those who received no induction (4). Perhaps more notably, there was no difference in death-censored graft loss or patient survival at one year compared to HIV-negative kidney transplant recipients also receiving ATG induction. Given that the outcomes of HIV-positive kidney transplantation, particularly in those who experience acute rejection, still appear inferior to those of age-matched non-HIV kidney transplant recipients, this analysis goes some way to support the use of ATG as induction in HIV-positive kidney transplant recipients.

Alemtuzumab (Campath 1H) is a lymphocyte-depleting agent directed at CD52 which profoundly depletes T and B lymphocytes. Several small randomised controlled trials, typically using tacrolimus monotherapy compared to standard care of IL-2RA combined with tacrolimus and mycophenolate, have shown broadly similar outcomes in terms of infection risk and long-term rejection rates. A recent randomised trial showed that, in comparison with basiliximab-based treatment, alemtuzumab-based induction therapy followed by reduced CNI and mycophenolate exposure and steroid avoidance reduced the risk of biopsy-proven acute rejection in a broad range of patients receiving a kidney transplant (5). However, while small numbers of HIV-positive patients have received alemtuzumab induction (6), there is currently insufficient evidence to recommend its use in this setting.

In short, the evidence base for the use of lymphocyte-depleting agents in HIV-positive kidney transplantation is very limited. Somewhat predictably, and in parallel with HIV-negative patients (7), $CD4^+$ counts are significantly and profoundly lower in patients who have received ATG (8), invalidating $CD4^+$ counts as a marker of HIV control in these patients, although viral load assays remain unimpaired. It would seem prudent to use these agents with considerable caution in patients who have had an AIDS-defining illness prior to control of their HIV and to ensure that appropriate prophylaxis against infections such as *Pneumocystis jirovecii* is extended until $CD4^+$ counts have recovered.

Belatacept is a selective T cell co-stimulation-blocker used as immunosuppressive agent and marketed to avoid or reduce CNI exposure. There is insufficient evidence to recommend its use in HIV-positive kidney transplant recipients, but the high rates of rejection associated with its use in the absence of CNI suggest that it would be inadvisable in HIV-positive patients who already appear to be at higher immunological risk.

12.2 Maintenance immunosuppression

In non-HIV kidney transplant recipients, there is good evidence to support the use of tacrolimus over ciclosporin in terms of reduced acute rejection and graft survival (9-11). There are some data to suggest that mycophenolate (at a daily dose of 2 g) is superior to azathioprine in preventing acute rejection, and possibly in terms of long term function (12). The Symphony study concluded that the best combination of maintenance immunosuppression in terms of reduced rejection and optimal graft survival was afforded by tacrolimus, mycophenolate and prednisolone in patients given IL-2RA induction (11).

There is some *in vitro* evidence to suggest that ciclosporin and in particular mTOR inhibitors may have an anti-HIV effect including, in the case of mTORs, decreased CCR5 expression and viral reactivation, which may be reflected *in vivo* (13). However, post-transplant viral reactivation seems rarely to be clinically significant in patients with well suppressed disease on a stable pre-transplant cART regimen, so there may be no significant advantage of this putative anti-viral effect. Moreover, US registry data suggest a relative risk of acute rejection of 2.2 at one year for mTOR-based regimens implying, albeit on the basis of small numbers, that these agents alone may not be sufficiently immunosuppressive in this population (4).

To date there are insufficient data in HIV-positive patients to make absolute recommendations on the best maintenance immunosuppressive regimen. However, given the high rejection rates in HIV-positive kidney transplantation, it would seem prudent to recommend what appears to be the most effective combination in non-HIV kidney transplantation, namely the combination of tacrolimus, mycophenolate and prednisolone. The HIV-TR Investigators study suggested that tacrolimus was better in this population, with an increased rate of acute rejection in patients treated with ciclosporin compared with tacrolimus (HR 9.2), and also suggested that mycophenolate mofetil was protective (1).

The addition of steroids to this regimen depends on the perceived immunological risk and for many low risk patients the threat of NODAT and other side effects of steroids may outweigh the risk of acute rejection. Co-infection with hepatitis B and C is relatively common in the HIV-positive population and, because of steroid response elements in the promoter region of hepatitis B (and to a lesser extent hepatitis C) virus, steroid avoidance in this subset of patients seems attractive. However, in a small series of HIV-positive kidney transplant recipients treated with basiliximab and methylprednisolone for 5 days followed by a calcineurin inhibitor plus mycophenolate, unacceptably high rates of acute rejection (61.5%) were observed (14) suggesting that the benefits of steroid-free immunosuppression in HIV-infected kidney transplant recipients may be outweighed by the high rate of acute rejection.

12.3 Management of acute rejection

In the non-HIV kidney transplant population, the treatment of acute rejection has rarely been subject to randomised controlled trials but a general consensus has arisen that the initial treatment of acute T-cell mediated (cellular) rejection should be with corticosteroids with an increase in background immunosuppression (12). Failure to control acute cellular rejection usually involves escalation to lymphocyte-depleting antibodies or, if there is antibody-

mediated rejection, consideration of plasma-exchange, anti-CD20 monoclonal antibody or intravenous immunoglobulin, with or without lymphocyte-depleting agents (12). The evidence base for any treatment beyond pulsed corticosteroids and augmented background immunosuppression is very weak and, in the HIV kidney transplant setting, merely extrapolation. However, there is no reason to suppose that HIV-positive kidney transplant recipients are at higher risk from pulsed corticosteroids and this would therefore seem appropriate first line treatment. Previous guidelines have shied away from the use of lymphocyte-depleting agents in HIV-positive kidney transplant recipients (3) but, as stated above, there is growing evidence that ATG at least can be used relatively safely in this population (4). Ultimately the decision to treat rejection with a lymphocyte-depleting agent is complex and depends on the quality of the transplanted organ and the robustness of the recipient.

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13. POST-TRANSPLANT PROPHYLAXIS

Recommendations

We recommend that HIV-positive transplant recipients receive lifelong prophylaxis against *Pneumocystis* pneumonia following transplantation (1D)

We suggest that *Toxoplasma* IgG seropositive recipients with a $CD4^+$ count <200 cells/μL or any recipient of an organ from a donor seropositive for toxoplasmosis receive lifelong prophylaxis (2C)

We recommend that prophylaxis against cytomegalovirus is indicated in CMV seronegative recipients of organs from CMV seropositive donors for a minimum of 3 months (1A)

We recommend that CMV seropositive transplant recipients receive either prophylaxis against CMV infection or PCR surveillance and pre-emptive therapy for a minimum of 3 months (1A)

Transplant patients who are well and were not assessed and treated for *Mycobacterium tuberculosis* latent infection or disease before transplantation should be assessed as recommended for patients prior to transplantation (1C)

Transplant patients who are well and were assessed and treated for *Mycobacterium tuberculosis* latent infection or disease before transplantation do not need re-assessment for *Mycobacterium tuberculosis* latent infection unless there is a new history of exposure to tuberculosis (1C)

Transplant patients who are re-exposed to tuberculosis after transplantation should be assessed for *Mycobacterium tuberculosis* latent infection and/or disease as recommended in current NICE TB guidance on tuberculosis contact tracing (1C)

We suggest that where there is a reliable prior history of treated TB infection there is no need for further testing beyond symptom review and chest X-ray, and these individuals do not require TB prophylaxis unless TB re-exposure is suspected (2D)

We suggest that prophylaxis against *Mycobacterium avium* complex (MAC) is indicated when the $CD4^+$ count is ≤ 50 cells/μL, and it be stopped when the CD4 count is >100 cells/μL for 6 months (2D)

Rationale

HIV-positive patients undergoing transplantation are assumed to have an augmented risk of developing opportunistic infections due to exogenous immunosuppression and may therefore require more stringent prophylactic regimens than in the HIV-negative transplant recipient, although strong evidence to support this assumption is lacking (1). Indeed, there are relatively few reports of HIV-associated opportunistic infections post-transplantation.

13.1 *Pneumocystis* pneumonia (PCP)

In general, anti-*Pneumocystis* prophylaxis is recommended for all non-HIV-infected solid organ transplant recipients for at least 3-6 months post-transplant, though longer durations may be considered (2). The HIV-TR protocol called for lifelong *Pneumocystis* prophylaxis (3). Whether HIV-infected transplant recipients require this more aggressive approach is not known, although it is notable that most studies report low incidences of opportunistic infections using this strategy. In HIV infection the risk for PCP is linked to $CD4^+$ counts <200 cells/μL, or less than 20% of the total circulating lymphocyte pool (4), so unless lifelong prophylaxis is given it would be prudent to restart prophylaxis if the $CD4^+$ count falls below this level. The drug of choice for prophylaxis is trimethoprim-sulfamethoxazole (co-trimoxazole) 480 mg once daily. Co-trimoxazole also provides protection against *Nocardia* and toxoplasmosis (see below). The second-line agent for PCP prophylaxis is either aerosolized pentamidine 300 mg via nebulizer monthly or dapsone 100 mg once daily, although the latter is contra-indicated in glucose-6-phosphate dehydrogenase deficiency. In the case of co-trimoxazole or dapsone allergy, consider atovaquone 1500 mg once daily or.

13.2 *Toxoplasma gondii*

Toxoplasmosis in transplant recipients can occur through ingestion of contaminated food or water, after receiving an infected allograft, or by reactivation of latent infection. To avoid primary infection, transplant recipients should avoid contact with undercooked meat, soil,

water or animal faeces that might contain toxoplasmosis cysts. The routine use of co-trimoxazole for post-transplant PCP prophylaxis has decreased the risk of toxoplasmosis and is the most effective prophylaxis against this parasite, although the optimal dose and duration remains unclear. In HIV-positive patients, co-trimoxazole 960 mg once daily is recommended as first line prophylaxis (5), although many studies show successful prophylaxis using co-trimoxazole 960 mg thrice weekly for varying durations. An alternative that has been well studied in patients with HIV/AIDS is dapsone 50 mg once daily plus pyrimethamine 50 mg once weekly. Pyrimethamine is typically given with folinic acid. Atovaquone 1500 mg once daily with or without pyrimethamine is likely to be effective as well. There are reports of toxoplasmosis after stopping prophylaxis in high-risk patients, so lifelong prophylaxis is recommended for *Toxoplasma* IgG+ subjects with a $CD4^+$ count <200 cells/µL, or any recipient of an organ from a donor seropositive for toxoplasmosis.

13.3 Cytomegalovirus

In the absence of data specific to HIV-positive recipients, CMV prophylaxis guidelines applicable to HIV-negative patients should be followed (6). The two major strategies for CMV prevention are antiviral prophylaxis and pre-emptive therapy (7). Each has advantages and disadvantages and both are similarly effective for the prevention of CMV disease. Many centres prefer prophylaxis to pre-emptive therapy for the highest risk, namely CMV donor-seropositive, recipient-seronegative (D+/R-), individuals. Valganciclovir is the preferred prophylactic agent, and in general should be started as early as possible and within the first 10 days after transplantation. The duration of prophylaxis depends on the CMV donor and recipient serology, but in a non-HIV-infected patient population there is some evidence to suggest that extending the duration of antiviral prophylaxis from 3 months (100 days) to 6 months (200 days) in CMV D+/R- kidney recipients may reduce the incidence of CMV infection and disease (8). As a group more susceptible to infection and likely to be receiving augmented immunosuppression, 200 days may be preferred.

13.4 *Mycobacterium tuberculosis* (TB)

It is important to document pre-transplantation treatment for latent MTB or active disease and obtain relevant records. Individuals having a reliable prior history of treated latent TB infection or treated TB disease need not undergo TST or IGRA. However, these individuals

should undergo symptom review and chest X-ray, followed by additional testing to screen for active TB only if indicated by new exposure to TB.

Transplant patients who have not been assessed and treated for latent TB infection or disease should be assessed for these conditions in accordance with NICE guidance (9).

13.5 Non-tuberculosis mycobacteria (NTM)

The common NTM causing infection following transplantation include *Mycobacterium avium-intracellulare* complex (MAC)*, M. kansasii, M. marinum, M. haemophilum* and the rapidly growing mycobacteria (RGM): *M. fortuitum, M. chelonae* and *M. abscessus.* The most frequently encountered species causing pulmonary disease include *M. avium* complex*, M. kansasii, M. xenopi* and *M. abscessus* (10). Among HIV-infected persons, a $CD4^+$ T cell count of <50/µL is associated with increased risk of disseminated NTM infection. It is therefore suggested that prophylaxis against NTM is indicated when the $CD4^+$ T cell count is ≤50 /µL, and may be stopped when the $CD4^+$ count has been >100 cells/µL for 6 months. The preferred primary prophylaxis is with azithromycin 1250 mg once weekly; alternatively clarithromycin 500 mg twice daily or rifabutin 300 mg once daily. The preferred secondary prophylaxis is with azithromycin 500 mg once daily in combination with ethambutol 15 mg/kg/day; alternatively, clarithromycin 500 mg twice daily plus ethambutol 15 mg/kg/day. The regimen may be modified based on previous MAC treatment. Note that significant drug interactions exist between immunosuppressants and clarithromycin and rifabutin, and close monitoring of concentrations is required. If protease-inhibitors are co-prescribed, rifabutin should be administered at half the usual daily dose (i.e. 150 mg once daily). Note also that ethambutol requires dose reduction in renal impairment such that for a GFR between 10 and 20mL/min the dose should be reduced to 15 mg/kg every 24–36 hours, or 7.5–15 mg/kg/day and for a GFR below 10mL/min the dose should be 15 mg/kg every 48 hours, or 5–7.5 mg/kg/day.

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14. MONITORING ALLOGRAFT FUNCTION

Recommendations

We recommend that existing guidelines regarding post-operative care of the kidney transplant recipient are followed for all kidney transplant recipients with HIV disease (Not graded)

We suggest that local practice for monitoring of the pancreas allograft is followed (Not graded)

Rationale

There is no evidence that post-operative care should be different for HIV-infected and non-infected kidney and pancreas transplant candidates. Current UK guidance was published by the Renal Association in 2011 (1). For monitoring of virological control see section 15.

A recent study from France reveals the capacity of HIV-1 to infect the kidney allograft despite undetectable viraemia (2). Urine testing for HIV DNA and RNA levels appears to be a promising noninvasive method of diagnosing HIV-1 reinfection, although this remains to be confirmed in a larger cohort. These data strongly support the need for close proteinuria monitoring in assessing the outcome of HIV-infected kidney transplant recipients.

Specific follow up of the pancreas allograft varies widely across the UK, and we recommend that local practice is followed.

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15. MONITORING OF HIV VIROLOGICAL CONTROL

Recommendations

We recommend that quantitative HIV RNA and CD4+ T-cell counts are measured regularly, with the first assays at 1 month after transplant and subsequent studies every 2-3 months for the first year and every 3-6 months thereafter (1B)

We suggest that more frequent monitoring of CD4 count may be necessary in patients receiving depleting antibodies to determine the need for anti-infective prophylaxis (2D)

We recommend that if patients have persistent HIV viraemia, drug-resistance testing is carried out to determine treatment options (1D)

Rationale

While most studies have not shown HIV-disease progression to AIDS or an increase in HIV-associated opportunistic infections following transplantation, some studies have shown that CD4+ cell counts can be affected depending on the type of immunosuppressive agents used. In the HIV-TR study, the use of thymoglobulin was associated with a greater decline in $CD4^+$ T-cells in the first year after transplant when compared to kidney recipients who did not receive thymoglobulin induction (1). However, at 3 years post-transplant there was no significant difference between the two groups.

Anti-viral treatment that is insufficient to completely suppress viral replication imposes a selective pressure that may result in the emergence of drug-resistant viral escape mutants. HIV drug resistance testing is thus part of the standard management of patients in whom viral replication is not suppressed (2).

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16. CHOICE OF LIVING VERSUS DECEASED KIDNEY DONOR

Recommendations

We recommend that patients with HIV infection have the same access to living donor kidney transplantation as non-infected patients (1B)

We suggest that potential donors for patients with HIV infection are informed of medical, surgical, and psychosocial factors that may heighten the recipient's morbidity and mortality risk but that disclosure of the recipient's HIV status is not mandatory (Not graded)

We recommend that patients with HIV infection are unsuitable to be living kidney donors (1D)

Rationale

Living kidney donation yields superior outcomes relative to deceased donor transplantation (1). Nevertheless, HIV-infected patients may encounter unique barriers to living donor kidney transplantation. For instance, some patients and care providers may not recognize the favourable transplant outcomes for those with HIV and may not feel it is appropriate to ask others to consider living donation. Previous UK consensus guidelines required disclosure of HIV to potential living donors (2), causing reluctance in some patients because of concerns about social stigma. This recommendation has been softened in the most recent UK Living Donor Kidney Transplantation guidance (3).

A recent survey found that HIV-infected patients have less knowledge about living donor kidney transplantation, have more concerns about living donor kidney transplantation, and are less willing to pursue living donor kidney transplantation than those without HIV (4). Most perceive their HIV status to be a barrier to living donor kidney transplantation.

Most potential donors would not alter their donation decision if they learned that the intended recipient was HIV-infected (5). However, a majority of these same adults and former donors felt that the HIV status of intended recipients should be disclosed to potential donors. It is therefore important to work collaboratively with potential donors and recipients to ensure an informed risk-benefit assessment and there may be a need to tailor pre-transplantation

education to address the unique circumstances of this patient subgroup. For further discussion on this issue see section 17.

Given the increased risk of kidney disease in HIV-infected patients (6) the use of such patients as living kidney donors, even with well-controlled HIV, is not recommended.

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17. CONSENT AND CONFIDENTIALITY

Recommendations

We recommend that existing guidelines on the ethics of deceased donor and living donor transplantation are followed for all transplantation involving people with HIV disease (Not graded)

We recommend that the standard of consent for HIV-positive transplant candidates is the same as for any other transplant (Not graded)

We suggest that, wherever possible, the recipient is encouraged to disclose their diagnosis of HIV to their donor (Not graded)

We suggest that all living donors are asked whether there are any medical conditions that would cause them to change their decision to donate, without highlighting HIV (Not graded)

We suggest that all living donors are made aware that there may be medical and social information about the recipient that is not disclosed (Not graded)

We suggest that all living donors are asked to acknowledge that they are aware that they will not be given confidential information about the recipient which is not deemed relevant to the outcome of the kidney transplant (Not graded)

We recommend that transplant teams must be satisfied that donor consent is adequate and that procedures for ensuring this are transparent and established in advance (Not graded)

Rationale

17.1 Existing guidelines

All health professionals involved in transplantation should acknowledge the wide range of complex moral issues that are associated with this area of clinical practice and ensure that good ethical practice consistently underpins clinical practice to achieve optimum outcomes

(1,2). The BTS Ethics Committee is able to provide additional support and advice where required.

17.2 No longer an 'experimental' procedure

Previous guidelines have stated that transplantation for recipients who have HIV disease should be explicitly described as 'experimental' or 'new' (3-5). There is now sufficient evidence to suggest that transplant outcomes for recipients with HIV are comparable to those of people with other co-morbidities such as diabetes (6). It is a fundamental part of consent for any procedure that the risks and benefits be understood in order for consent to be adequate (7,8). There are now sufficient data for those risks and benefits to be discussed when seeking consent to donation and transplantation for patients with HIV in the same way as they should be for patients with other co-morbidities (9).

17.3 Particular issues relating to the disclosure of a diagnosis of HIV in living donation

Living kidney donation may introduce potential conflict between donor consent and recipient confidentiality because of the stigma attached to HIV disease. Although the surgical risks associated with organ donation are unchanged for the potential donor regardless of the identity of the recipient, the likelihood of transplantation being successful may inform the donor's decision to donate. If it is established that information regarding the likelihood of success would influence an individual's decision to donate, providing accurate information becomes an integral part of the consent process (10). In order to discuss the likelihood of success of transplantation, including recipient mortality or morbidity and/or graft survival, it is most desirable to have consent from the recipient to openly discuss their medical conditions. We therefore suggest that, wherever possible, the recipient should be encouraged to disclose their diagnosis of HIV to their donor.

For some individuals, the disclosure of a diagnosis of HIV may have harmful consequences. We suggest that it is possible to provide adequate information about the likelihood of success and the possible outcomes of transplantation without reference to particular conditions. On that basis, disclosure of the recipient's diagnosis of HIV is, whilst preferable, not essential for the donor to be able to provide informed consent (11).

While transplant teams have a legal and moral duty to treat people with HIV without discrimination, potential donors have no such obligation. They can change their decisions about donation for any reason. In order for donor consent to be adequate without discussion of specific medical conditions, transplant teams should confirm with the donor which conditions, if any, would cause them to change their decision to donate. We therefore suggest that all living donors should be asked whether there are any medical conditions that would cause them to change their decision to donate, without highlighting HIV. Ideally, this should happen as part of general discussion about potential donors' preferences for information early in the process.

We suggest that all living donors are made aware that, whilst the recipient has undergone an extensive medical and psychosocial evaluation and has been found to be an appropriate candidate for renal transplantation, there may be medical and social information about the recipient which is not disclosed. We suggest that all living donors are asked to acknowledge that they are aware that they will not be given confidential information about the recipient which is not deemed relevant to the outcome of the kidney transplant (12). This should be recorded rather than merely acknowledged, in case of subsequent challenge.

17.4 Confidence of the transplant team in the consent process while respecting recipient and donor confidentiality

We recommend that transplant teams must be satisfied that donor consent is adequate and that procedures for ensuring this are transparent and established in advance. These procedures should not be at the expense of confidentiality (12). There may be occasions when a recipient's insistence on confidentiality means that it is felt that adequate consent cannot be obtained from a potential donor. On the other hand, refusal of a recipient to disclose their diagnosis of HIV need not automatically exclude the possibility of donor consent.

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18. USE OF HIV-INFECTED DONORS FOR HIV-INFECTED RECIPIENTS

Recommendations:

We recommend that transplantation using organs from HIV-infected individuals is restricted to organs from deceased donors with:

- **HIV viral load <50 copies/mL and CD4 count >200/µL for at least 6 months prior to brain injury**
- **Information about the donor virus such as historical genotype patterns where possible and current viral load**
- **No history of virological failure or drug resistance (1D)**

We recommend that recipients are counselled and give informed consent both at the time of listing and at the time of transplantation (1D)

We suggest that HIV+ organ use is restricted to those centres that have experience in transplanting HIV+ patients (Not graded)

We recommend that patients with HIV-infection are unsuitable to be living kidney donors (1D)

Rationale

HIV-infection is regarded as an absolute medical contra-indication to organ donation by many transplant centres. However, advances in care for patients with HIV, increasing waiting times, and reports of organ donation from HIV-infected (but treatment-naïve or receiving only first line ART) individuals in South Africa showing favourable outcomes at 3 to 5 years (1, 2), suggest that this approach should be reconsidered (3).

Clinical considerations include the risk of recipient super-infection with recombinant virus or virus from a different clade, with loss of virological control or transmission of viral resistance, although this may be unfeasible to characterise prior to donation. In order to address this, only donors who are fit but treatment-naïve or with well-controlled non-resistant virus should be considered. If possible, donor genotypic testing to confirm lack of resistance should be

performed. The recipient should be counselled about the risk of transmission of viral resistance.

A further consideration is the risk of transmission of opportunistic infection from the donor. To minimise this risk, only donors with well-controlled HIV and complete immune reconstitution should be considered. A robust donor CD4 count could be a surrogate marker for this, but the risk of transmission of opportunistic infection should be included in recipient counselling and consent. Currently a poorer outcome might be expected from HIV/HCV co-infected donors so these should not be used.

Finally, HIV infection can cause organ damage such as chronic kidney disease due to HIV-associated nephropathies (4), and the recipient should be counselled about this risk. Pre-implantation biopsies may be considered to detect donor disease.

There is in addition a small risk of organ misallocation leading to transmission of HIV to uninfected recipients, but this risk should be minimal under current patient selection and organ allocation policies.

Given the increased risk of kidney disease in HIV-infected patients, the use of such patients as living kidney donors, even with well-controlled HIV, is not recommended.

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