

# HIV, HBV and HCV infection

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## GUIDELINES

### a. HIV

- i. Testing for HIV should be performed in all potential kidney transplant candidates (Ungraded)
- ii. We recommend that HIV infection should not preclude a patient from being assessed for kidney transplantation (Level 1D)

### b. HBV

- iii. Testing for HBV should be performed in all potential kidney transplant candidates (Ungraded)
- iv. We recommend that HBV infection should not preclude a patient from being assessed for kidney transplantation (Level 1D)

### c. HCV

- i. Testing for HCV should be performed in all potential kidney transplant candidates (Ungraded)
- ii. We recommend that HCV infection should not preclude a patient from being assessed for kidney transplantation (Level 1D)

## SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

### HIV

- **Assessment of HIV-infected potential kidney transplant patients should be performed in centers with experience in the management of both HIV infection and kidney transplantation.**
- **HIV-infected patients may be candidates for kidney transplantation if the following criteria are met:**
  - i. **Adherence to a HAART treatment protocol, with no recent change to anti-retrovirals within 3 months**
  - ii. **Undetectable viral load for at least 3 months**
  - iii. **CD4 count >200/ $\mu$ L for at least 6 months**
  - iv. **Patients with no history of a detectable HIV RNA test and who maintain undetectable HIV RNA levels without HAART may be suitable for transplantation**
  - v. **Some previous opportunistic complications may exclude transplantation**
  - vi. **Other usual kidney eligibility criteria are met**
- **HIV patients co-infected with HCV or HBV may be suitable for kidney transplantation. Both infections should be fully assessed. Those patients with cirrhosis and HCV or HBV co-infection may be considered for a combined liver/kidney transplant in some circumstances.**

### HBV

- **Renal transplant candidates with HBV infection should undergo complete specialist hepatology assessment.**
- **Potential transplant recipients with decompensated HBV cirrhosis may be considered for a combined liver/kidney transplant.**
- **Transplant candidates with HBV liver disease should be treated, if suitable (chronic active hepatitis, compensated cirrhosis).**

- **Patients with no response to HBV treatment may still be considered for transplantation in some circumstances.**

#### **HCV**

- **The KDIGO clinical practice guideline for the prevention, diagnosis, evaluation and treatment of Hepatitis C in Chronic Kidney Disease provide recommendations and suggestions appropriate to consideration of kidney transplant recipients within Australia and New Zealand (INSERT LINK). Specifically, for the HCV-infected potential kidney transplant recipient;**
  - i. HCV RNA positive infected patients being considered as candidates for kidney transplantation should undergo specialist hepatology assessment. If suitable treatment with anti-viral medication should be undertaken prior to transplantation.**
  - ii. HCV infected patients with cirrhosis and compensated liver disease may be considered for transplantation in some investigational circumstances**
  - iii. HCV infected patients with cirrhosis and decompensated liver disease may be candidates for combined liver/kidney transplantation.**

### **IMPLEMENTATION AND AUDIT**

- The proportion of patients who are candidates for kidney transplantation whose status for HIV, HBV and HCV is known should be monitored. The prevalence of these infections and changes with time should be tracked at the individual unit level. There are no mechanisms at present to ensure implementation or audit this practice at a national level.
- Prospective information regarding the HIV, HBV and HCV status of those on renal replacement therapy and those patients undergoing transplantation is important. This is not currently collected or reported. There are no mechanisms currently to implement or audit these data (see below).

### **BACKGROUND**

Concerns regarding infectious complications exacerbated by immunosuppression after transplantation have led to the widespread screening of all potential renal transplant candidates for evidence of active infection. Often, however, these infections can be adequately managed to allow successful transplantation [1-3]. This guideline was designed to focus on chronic viral infections (HIV, HBV and HCV) which are increasingly recognized amongst potential transplant recipients and may be modified to safely allow transplantation.

This guideline reviews the optimal approach to HIV, HBV and HCV amongst those patients being considered for listing as candidates for renal transplantation. It is focused on these chronic viral infections, in particular, because each has relevant therapeutic interventions which may be undertaken to potentially reduce morbidity and mortality after renal transplantation. It is designed specifically to ensure that all patients with these conditions are considered for renal transplantation, which can improve their clinical outcomes compared to remaining on long-term dialysis.

### **SEARCH STRATEGY**

**Databases searched:** MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for HIV, Hepatitis B, Hepatitis C and then combined with a sensitive search strategy for cohort studies, incidence, prognosis, survival analysis, mortality, morbidity and quality of life. The search was carried out in Medline (1950 – September Week, 2 2009). The Cochrane Renal Group Trials Register was also searched for studies not indexed in Medline.

**Date of search/es:** 21 September 2009.

## **WHAT IS THE EVIDENCE?**

There is a large body of evidence to suggest that chronic viral infections are not a contraindication to transplantation. Increasing numbers of patients with HIV, HBV and HCV have been successfully transplanted. Data is now available suggesting that, for each of these infections, specialized assessment and management is mandated to optimize outcomes [1-3]. This guideline was designed to summarize the best available evidence for the approach to HIV, HBV or HCV-infected renal transplant candidates. Certainly, each transplant patient requires careful individual assessment and management. Ultimately, some may remain untransplantable; however, for many the benefits of transplantation will still outweigh the risks.

Because of the nature of this area no randomized clinical trials exist. This data consists of retrospective and prospective cohort studies, case series and case reports. The evidence for each virus will be considered in turn, with separate consideration then given to co-infected patients.

### **HIV infection**

#### **Should an HIV-infected patient be considered for transplantation?**

The question of the appropriateness of renal transplantation amongst the HIV-infected population is important, given that HIV patients are at particular risk of renal disease [4, 5]. The prevalence of renal disease related to HIV continues to increase, even with the widespread use of HAART [6]. Of relevance is the increasing age and associated co-morbidities of the longer-surviving HIV infected population, as well as the description of the nephrotoxic nature of some anti-retrovirals [7]. As well, frequent co-infection with hepatitis viruses and the association with the metabolic syndrome may at least partially explain the high frequency of renal disease observed [8, 9]. HAART has rapidly and profoundly changed the phenotype of renal disease observed amongst the HIV-infected cohort. The consequence of the marked alteration in aetiologies of renal disease in the HIV infected cohort has been the increasing emergence of kidney disease in those patients with excellent control of HIV replication. Some of these patients exhibit new renal side effects related to antiretroviral therapy [10].

The ability to suppress HIV infection and the consequent improvement in survival rates has lead to the widespread use of transplantation in these patients. Recent data concerning renal transplantation report equivalent outcomes to non-infected patients in highly selected transplant candidates [11]. Data prior to the HAART era also suggested acceptable outcomes in some patients; however, other reports were less favorable. [4, 12, 13]

Additionally, the outcomes of HIV-infected patients on dialysis are poor [14]. Studies prior to the advent of HAART demonstrated worse patient survival with dialysis amongst those with HIV than without [15]. In the post-HAART era, outcomes on dialysis still remained poor, with the numbers of patients requiring treatment for end-stage renal disease increasing [3]. The adverse outcomes seen with dialysis amongst these patients was a primary impetus leading to the reevaluation of the role of transplantation. Exact numbers of HIV-infected patients on dialysis, with a functioning transplant or being considered for renal transplantation within Australia and New Zealand are presently unknown.

Successful renal transplantation has; however, been undertaken in such patients in both countries [16].

Given the rapid changes in the management and outcomes of HIV infected patients, guidelines suggesting HIV infected patients be excluded from transplant programmes are outdated. Emerging evidence reinforces the excellent outcomes that are possible in these patients.

The first small prospective study of outcomes of renal transplantation in the HAART-era reported equivalent one year graft and patient survival to the non-infected cohort. These patients exhibited stable HIV with undetectable viral load and an absence of opportunistic infections. Importantly, a higher rate and severity of acute rejection was demonstrated in these patients [12].

Subsequent studies include case reports, retrospective studies and small prospective cohort studies [13, 17, 18]. These studies primarily focused on a selected cohort of patients with well controlled HIV-infection. These small studies demonstrated similar patient and graft survival rates to uninfected patients. A higher rate of acute rejection episodes was again observed. As well, Roland's prospective study including outcomes at 3 years post-transplantation demonstrated high rejection rates with encouraging graft survival rates [19].

Other studies also report encouraging results, with comparable patient and graft survival rates to non-HIV infected patients [11, 20-23]. Stock et al have reported similar findings in their prospective observational trial [24]. In this study both patient and graft survival rates were excellent at 1 and 3 years with no increase in HIV-related complications seen. High acute rejection rates were observed once more in this cohort.

### **What criteria should be used to select a patient with HIV on to the renal transplant list?**

Overall, careful selection and specialized management of these patients appears important. In particular, medication dosage errors are common and antiretrovirals are often wrongly prescribed [25]. This is in addition to the other complexities required in the assessment and management of both the HIV-infection as well as emerging co-morbid conditions.

The criteria for acceptance of HIV-infected patients on to the renal transplant wait-list are under active investigation with large cohort studies such as the Solid Organ Transplantation in HIV Multi-Site Study [26]. It is accepted that HIV infection should be suppressed with undetectable HIV RNA, and that there is evidence of successful immune reconstitution after HAART. Minimum criteria for acceptance to the renal transplant waiting list usually include:

- i. Stable HAART regimen
- ii. Undetectable viral load for over three months
- iii. CD4 T lymphocyte count > 200/ $\mu$ L
- iv. Otherwise suitable for renal transplantation

There is some variability in these requirements between centers, with some mandating longer periods of excellent viral control. Overall, there appears to be a move toward greater flexibility within these criteria and a liberalization of restrictions.[23, 26-29]

Many other variables have been used as criteria for acceptance to the renal transplant waiting list, including;

- i. No history of progressive multi-focal leucoencephalopathy, opportunistic lymphoma (CNS or Burkitt) or chronic cryptosporidiosis for over one month's duration.
- ii. No therapy with IL-2 or GM-CSF in the previous six months
- iii. Potential drug interactions manageable, with options for antiretroviral therapy post-transplantation
- iv. Careful assessment of HBV/HCV co-infection (see below)

- v. Treated Kaposi's sarcoma, BCC's or SCC's of the skin or solid tumors treated with curative therapy and a disease free duration of at least five years
- vi. If a history of pulmonary coccidioidomycosis, then the patient should have been treated and have remained disease free for at least five years

The absolute criteria permitting transplantation remain to be defined in this rapidly evolving area; however, there is a trend toward liberalization, given the excellent outcomes observed. Generally, a history of opportunistic infections is not an automatic exclusion criterion, as it once was [4]. As well, patients not on HAART with no history of a positive HIV RNA test and undetectable viral load for at least 3 months have also been transplanted with successful outcomes [26].

The assessment and management of HIV-infected renal transplant candidates is predominately undertaken at centers with extensive experience in both fields. Assessment and ongoing involvement of these patients by a team familiar with both conditions is important, and the absence of such a team has been used as exclusion criteria by many centers. Given the complexity of both conditions the early involvement of both the transplant team and the HIV medical care provider is logical, particularly given the complex interactions which may arise in the post-transplant period [30].

## **HBV infection**

### **HBV and assessment for renal transplantation**

HBV infection in haemodialysis patients may often be subclinical, and is usually an asymptomatic chronic disease [31]. The impact of HBV status and survival on dialysis is controversial and remains poorly characterized [32]. Progression of HBV related liver disease may be promoted by several factors amongst the dialysis population including; HCV co-infection, alcohol abuse and immunosuppression [33]. Overall, the prevalence of HBV has declined amongst the dialysis population because of routine vaccination, widespread awareness and improved infection control measures. The course of HBV infection after transplantation may be problematic, and may be associated with significant morbidity and mortality [34]. The systematic review and meta analysis of observational studies by Fabrizi et al [35] compared patient and graft survival between HBsAg+ and HbsAg- kidney transplant recipients. The summary estimate for relative risk of death after transplant was 2.49 (95% CI:1.64-3.78) for HBsAg+ compared to HBsAg- recipients, while the relative risk for graft survival was 1.44 (95% CI: 1.02-2.04). These risks may be minimized using newer approaches, outlined below.

Overall, the potentiation of HBV-related complications by initiating immunosuppression with renal transplantation remains important, and mandates that these patients be carefully assessed and counseled about these risks. It may be difficult to know, however; in the modern era whether the survival advantage conferred by transplantation is outweighed by the risk of progressive liver disease in some cases [36]. Older studies may not take in to account new factors such as widespread availability of viral replication testing, Lamivudine therapy, assessment of liver histology and other factors effecting post-transplant outcome.

It is difficult to predict those patients who may be at particular risk of morbidity and mortality with transplantation; indeed, most patients with HBV demonstrate enhanced viral replication under the influence of steroid therapy [37]. Patients with persistent viral replication are at high risk for liver disease [38]. Safe and effective anti-HBV therapies and an understanding that overall mortality in non-cirrhotic HBV-infected renal transplant recipients is no different from non-infected patients [39], has meant that HBV-infected patients are routinely transplanted in Australia and New Zealand, providing that these patients are carefully assessed and selected prior to transplantation [40].

### **Evaluation of the HBV-infected renal transplant candidate**

Because of the possible adverse effects on outcomes of HBV with the use of immunosuppression the severity of liver disease and an approach to its management should be formulated in the pre-transplant candidate to attempt to ensure optimal outcomes [40]. In particular, in patients on dialysis,

even those with few clinical markers suggesting significant liver disease, may have a significant underlying burden [32, 41]. All HBV infected renal transplant candidates (HBsAg+) should undergo liver biopsy to exclude underlying cirrhosis.

Those patients with established cirrhosis are complex, and decisions regarding their ongoing management are difficult [38]. Those patients with decompensated cirrhosis should be considered for a combined liver-kidney transplant. Assessment for this procedure is generally undertaken at a large centre with experience in both procedures.

All patients with HBV are at risk for progression of disease in the setting of immunosuppression. New antiviral therapies may be able to reduce this risk [33]. The evidence base for decisions regarding antiviral therapy amongst patients with end stage renal disease is not strong, and the area is evolving with new treatments and new management approaches. Patients that do not meet current conventional indications for initiation of therapy are still being offered treatment in some circumstances [42]. Those with active viral replication seem to be particularly at risk for progressive disease, and should be treated prior to transplantation. Those with no markers of viral replication are; however, still at risk of reactivation of HBV post-transplantation. These risks may be minimized with the use of antiviral therapies around the time of transplantation.

## **HCV infection**

### **HCV and assessment for renal transplantation**

The hepatitis C guideline from KDIGO [1] is an extensive review of the current evidence for the prevention, diagnosis, evaluation and treatment of Hepatitis C in Chronic Kidney Disease. It contains specific recommendations regarding the management of HCV-infected patients before and after transplantation (Guideline 4). This guideline was acknowledged by ANZSN and CARI in 2009 [43].

Tables from the KDIGO guidelines [1] have been reproduced in the Appendix to this guideline. Table 22 presents a summary of studies of patient mortality in HCV positive transplant recipients compared to wait-listed HCV-positive haemodialysis patients while Table 23 presents a summary of outcomes of HCV-positive compared to HCV-negative transplant recipients.

HCV is common, and may be present in 2-50% of renal transplant recipients or dialysis patients [37]. Hepatitis C has been demonstrated to negatively affect outcomes after transplantation, and is associated with increased graft loss, sepsis, progressive liver disease and post-transplant diabetes, amongst other complications [44]. Some of these may be attributable to immune effects of HCV infection, with disruption of normal cellular immunity. Careful selection and appropriate management of these patients prior to transplantation is essential. Patients who are fully assessed and are considered appropriate for transplantation demonstrate very low rates of progressive liver injury [45, 46].

### **Evaluation of the HCV-infected renal transplant candidate**

Because of the adverse effects on long-term outcomes and differences in patient management according to the severity of liver disease, an approach to the patient with HCV being considered for a renal transplant should be formulated prior to transplantation. This is usually in conjunction with specialized Hepatology units, who are experienced in this field. It may also be possible to manage the HCV prior to transplantation, improving patient outcomes.

As with hepatitis B in renal patients, there is a poor correlation between serum alanine aminotransferase levels and clinical activity of HCV-related liver disease [38]. All anti-HCV+ patients should be tested for the presence of HCV RNA in serum to assess for active HCV infection. Most anti-

HCV+ dialysis patients will demonstrate sero-positivity for HCV-RNA [47]. Those patients who are anti-HCV+ but HCV RNA negative may have previously eradicated the virus, and demonstrate a very small risk of reactivation [48]. Liver biopsy is essential in those patients with active HCV replication (HCV RNA positive). This allows the underlying severity of disease that is present to be established. Despite normal serum aminotransferases many of these patients will have significant liver disease [48]. Liver biopsy is not necessary if there are clinical, radiological or laboratory markers of cirrhosis or portal hypertension. The risk of biopsy-related hemorrhage is high in these patients.

The assessment of these patients is generally undertaken in a specialized unit with experience in the area. The individual management may vary, particularly in view of emerging therapies and new clinical approaches. Those patients with compensated HCV-related cirrhosis, in particular, may be transplanted in some circumstances being mindful of the risks associated with this approach.

### **Co-infected patients**

HIV infected patients who are co-infected with HBV or HCV are common, and deserve separate consideration because their management is different and their clinical outcomes may be inferior. [4] As many as 30% of HIV infected patients were also co-infected with HCV in one study [49] and up to 10% were co-infected with HBV [50]. The extent of liver disease and the clinical circumstances of these patients require particularly stringent examination. Co-infection is associated with progressive liver disease, and inferior clinical outcomes. These risks may be negated with the use of HAART [51]. HBV resistance to Lamivudine may be seen in patients on Lamivudine-containing HAART regimens. This circumstance may necessitate the use of newer anti-HBV agents.

Optimizing the management of co-infected patients prior to transplantation may result in improved outcomes [52]. Acceptable results have been reported in carefully selected co-infected patients who have received a kidney transplant [4]. This is an emerging area for which the optimal clinical approach remains to be defined. Co-infected patients require careful assessment and a full evaluation of the possible impact of proceeding to transplantation. Successful transplantation is still possible in this patient population.

## **SUMMARY OF THE EVIDENCE**

There is increasing clinical experience and an emerging body of evidence to suggest that potential renal transplant recipients with chronic viral infections (HIV, HBV, HCV) are candidates for transplantation and in many circumstances will have outcomes equivalent to the non-infected population. These excellent outcomes require careful selection of these patients prior to transplantation. This will allow for the optimization of outcomes and a full assessment of the risks and benefits for each patient prior to proceeding with long-term immunosuppression in the setting of a chronic infection.

Because of the nature of this area no randomized control trials exist. Additionally, the assessment of the evidence and how it applies to each potential transplant candidate requires knowledge of the up to date developments in the field, with the rapid emergence of new treatments and approaches to management. Newer antivirals, specialized management in the pre- and post- transplant period and other developments mean that this is an emerging and evolving field.

Clearly, patients with HIV, HBV and HCV should be considered as candidates for renal transplantation with careful assessment, management and selection allowing for successful transplantation in many circumstances. Few absolute contraindications to transplantation relating directly to HIV, HBV and HCV remain, and transplantation can improve the prognosis of many of these patients compared to remaining on dialysis.

## WHAT DO THE OTHER GUIDELINES SAY?

### **Kidney Disease: Improving Global Outcomes:**

The KDIGO clinical practice guideline for the prevention, diagnosis, evaluation and treatment of Hepatitis C in Chronic Kidney Disease was published in 2008 [1]. Updates and commentary are available on-line at <http://www.kdigo.org/>. The guideline statements were formulated using a modification of the GRADE method and were rated as “strong”, “moderate” or “weak”. The sections of the KDIGO guidelines on HCV relevant to the potential kidney transplant recipient include:

1. Guideline 1: Detection and evaluation of HCV in CKD
  - a. 1.1.2 Testing for HCV should be performed in patients on maintenance haemodialysis and in kidney transplant candidates (Strong).
2. Guideline 2: Treatment of HCV infection in patients with CKD
  - a. 2.1.4 It is suggested that HCV-infected patients accepted for kidney transplantation be treated (Weak).
  - b. 2.2.3 For patients on haemodialysis dose-adjusted monotherapy with standard IFN is suggested (Weak).
  - c. 2.3.3 All patients with HCV should be followed for HCV-related comorbidities (Strong).
    - i. Patients who have evidence of cirrhosis should have follow up every six months (Strong).
    - ii. Annual follow up for patients without cirrhosis is suggested (Weak).
3. Guideline 4: Management of HCV-infected patients before and after kidney transplantation
  - a. 4.1.1 All kidney transplant candidates should be evaluated for HCV infection (Strong).
  - b. 4.1.2 HCV should not be considered a contraindication for kidney transplantation (Moderate).
  - c. 4.1.3 It is suggested that HCV-infected kidney transplant candidates undergo a liver biopsy before transplantation (Weak).
  - d. 4.1.4 It is suggested that those patients with biopsy-proven cirrhosis and clinically-compensated liver disease be considered for kidney transplantation only in an investigational setting (Weak).
  - e. It is suggested that HCV-infected kidney transplant candidates be considered for treatment with standard IFN before transplantation (Weak).
  - f. Patients on the kidney transplant waiting list should be monitored for HCV (Weak).
    - i. It is suggested any patient found to have HCV viraemia be placed on the interim list whilst evaluated fully (Weak).
    - ii. Patients who have previously received antiviral treatment should receive HCV-RNA testing at least annually. If these patients become viraemic it is suggested they be placed on the interim list whilst their liver disease is evaluated (Weak).
    - iii. It is suggested that HCV-infected patients who have previously undergone liver biopsy and failed or refused treatment should have repeat liver biopsy every 3 to 5 years whilst on the renal transplant waiting list (Weak).

There are no KDIGO guidelines regarding potential kidney transplant recipients who are infected with HBV or HIV.

### **Kidney Disease Outcomes Quality Initiative:**

Published a commentary of the KDIGO guideline for the prevention, diagnosis, evaluation and treatment of Hepatitis C in CKD focused on its application and implementation for patients with CKD in the United States (AJKD 2008). The KDOQI guidelines relevant to HCV and recipient suitability in the USA are summarized below:

1. Guideline 2 (weak): although the available evidence supporting HCV treatment is weak as applied to the US population, it favors treatment of kidney transplant candidates. The benefits of treatment should be weighed against risks, bearing in mind a possible delay in transplantation during the lengthy treatment course for HCV.

2. Guideline 4: This guideline was based on data from the US population. Relevant aspects include: 4.1.1 suggesting evaluation of all transplant candidates for HCV (strong). 4.1.2 Recommends that HCV should not be a contraindication for transplantation (moderate). 4.1.5 Treatment of all suitable transplant candidates is recommended (weak). 4.1.3 Liver biopsy is recommended for detection of cirrhosis amongst transplant candidates who are HCV positive (weak). Those patients with cirrhosis may still be candidates for kidney transplantation in certain circumstances (weak).

There are no specific KDOQI guidelines concerning the approach to those transplant candidates infected with HBV or HIV.

Up to date guidelines and commentary on the applicability of other international guidelines to the United States are available at: [http://www.kidney.org/professionals/kdoqi/guidelines\\_commentaries.cfm#guidelines](http://www.kidney.org/professionals/kdoqi/guidelines_commentaries.cfm#guidelines).

### **UK Renal Association:**

Guidelines endorsed by The UK Renal Association concerning the assessment of kidney recipient suitability can be found at: <http://www.renal.org/Clinical/GuidelinesSection/AssessmentforRenalTransplantation.aspx>.

These guidelines recommend that patients otherwise suitable for renal transplantation with evidence of chronic HBV, HCV or HIV infection should be managed according to British Transplantation Society (<http://www.bts.org.uk/transplantation/standards-and-guidelines/>) and European Best Practice Guidelines prior to transplantation. As mentioned below the EBPG were published in 2000, and state that HIV is an absolute contraindication to transplantation. However; the British Transplant Society endorses guidelines specifically for those potential kidney recipients who are HIV positive.[3]. These guidelines classified the levels of evidence using the same system as the CARI guidelines (level I to IV). The aspects of these guidelines governing recipient suitability were based on level III evidence. The key aspects of the HIV specific guidelines are:

1. Guideline 1. Any patient with end-stage renal disease with a life expectancy of at least 5 years is considered appropriate for transplantation.
2. Guideline 2. Specific HIV related criteria include:
  - a) CD4>200cells/uL for at least 6 months
  - b) Undetectable HIV viral load for at least six months
  - c) Adherence to HAART for at least six months
  - d) Absence of AIDS-defining illnesses following successful immune reconstitution after HAART.

### **Canadian Society of Nephrology:**

The Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation were published in 2005. The strength of the evidence was graded using the Canadian Task Force on Preventative Health Care System ( Grade A= good evidence, grade B= fair evidence, Grade C = conflicting evidence). Relevant aspects of these guidelines specifically pertaining to HBV, HCV and HIV are summarized below:

Liver disease:

1. Guideline 1. All transplant candidates should be screened for evidence of liver disease, including serological testing for HBV and HCV. Appropriate follow up testing should also be performed. (Grade C)
2. Guideline 2. Patients with liver disease should be evaluated and followed up by a gastroenterologist. (Grade C)
3. Guideline 3. Transplant candidates with cirrhosis should not be considered for kidney transplantation alone, but may be considered for combined liver-kidney transplantation. (Grade C)
4. Guideline 6. All transplant candidates infected with HBV should be assessed for evidence of active viral replication, and undergo liver biopsy. (Grade C)
5. Guideline 7. Patients with active liver disease from HBV should be treated in the pre- and post-transplant period. (Grade C)
6. Guideline 8. Patients with HCV should be considered for kidney transplantation. (Grade B)
7. Guideline 9. All transplant candidates with anti-HCV antibodies should be tested for HCV RNA and cryoglobulinaemia. (Grade C)

8. Guideline 10. HCV RNA positive patients with no evidence of cirrhosis should undergo pre-transplant liver biopsy. (Grade C)
9. Guideline 11. HCV-infected patients with active viraemia may be offered a kidney from a HCV-infected donor. (Grade B)
10. Guideline 12. Patients at high risk for hepatocellular carcinoma should be screened as part of their pre-transplant assessment. (Grade C)

Infections:

1. Guideline 1. Patients should be free of active infection, whether of viral, bacterial or fungal origin. (Grade B)
2. Guideline 7. HIV-infected patients with end-stage kidney failure may be considered for kidney transplantation if they meet the following criteria (Grade B):
  - a. Adherence to a HAART regimen
  - b. Undetectable viral load for greater than 3 months
  - c. CD4 lymphocyte count greater than 200/ml for at least 6 months
  - d. No opportunistic infections
  - e. Willingness to use prophylaxis against CMV, HSV, PCP and fungal infections
  - f. Freedom from neoplasia except BCC or SCC of the skin or in-situ HPV associated anogenital carcinoma
  - g. Other usual kidney transplant eligibility criteria are met.
3. Guideline 8. Kidney transplantation in HIV-infected patients should only be performed in centers where staff have extensive experience in the management of both HIV infection and kidney transplantation. (Grade C)

The Canadian Society of Nephrology has also formally endorsed the KDIGO guidelines for HCV in CKD (<http://www.csnscn.ca/english/professional%20practice/guidelines>).

**European Best Practice Guidelines:**

The EBPG have endorsed the KDIGO hepatitis C guidelines for the management of HCV-positive potential kidney recipients (NDT 2009).

The EBPG also acknowledge the European best practice guidelines for transplantation (<http://www.ndt-educational.org/guidelines.asp>). These guidelines were first published in 2000 with no recent update available (NDT, 2000). The evidence is classified into level A (RCT) level B (large open trials or small trials with consensus results) or level C (small or controversial studies, or expert opinion). The guidelines relevant to HBV and HIV include:

1. Guideline 1.4, Contraindications for transplantation. Absolute contraindications to renal transplantation include HIV (Level B)
2. Guideline 1.5.2, Infectious risk.
  - a. All transplant candidates should be tested for HBV (Level B).
  - b. Renal transplant candidates with active HBV viral replication should undergo complete assessment, including liver biopsy (level B).
  - c. Transplant candidates with cirrhosis should not be considered for isolated renal transplantation, but may be considered for a combined kidney/liver transplant (Level C).
  - d. Transplant candidates with active liver disease should be offered treatment. Patients without improvement after treatment may still be considered for transplantation (Level C).
  - e. Kidneys from HBV-infected donors may be offered to HBsAg-positive recipients or HBV immunized recipients with consent, and when permitted by law (Level C).

The exclusion of HIV-infected patients from transplantation is not concordant with more recently published guidelines. The acceptance of HIV-infected patients for transplantation is widespread, and based upon evidence of good clinical outcomes in the HAART era.

**International Guidelines:**

The International Society of Nephrology acknowledged the KDIGO clinical practice guidelines on Hepatitis C in CKD in 2008 (Nature Clinical Practice Nephrology August 2008). The ISN recommends

these guidelines for implementation by its members, and acknowledges their worldwide utility. The acknowledgment focused particularly on those guidelines with “strong” recommendations, as summarized below:

1. Guideline 2. All patients with HCV infection and CKD should be followed up for HCV-associated co-morbidities, and those patients with HCV and clinical or histological evidence of infection should be followed up every six months.
2. Guideline 4. All kidney transplant candidates should be tested for HCV.

The ISN does not currently endorse any specific guidelines concerning the HBV or HIV infected renal transplant candidate; however, reference to the EBPG is made on the ISN website (<http://www.isn-online.org/isn/education/guidelines/guidelines.html>). Additionally, the ISN references the European Society of Urology guidelines for renal transplantation (<http://www.uroweb.org/nc/professional-resources/guidelines/online/>).

## **SUGGESTIONS FOR FUTURE RESEARCH**

1. Data could be sought on a national level through an organization such as ANZDATA, recognizing the resource limitations and the many demands already placed upon that organization. There is limited space available for reporting on individual patients’ ANZDATA forms. Currently, HCV status is specifically collected; however, HCV status is not feed back as part of the annual ANZDATA report. Specific questions do not currently exist for HBV or HIV status on the form, but may be entered on an ad hoc basis under the “other co-morbid conditions” section. The present approach may result in an under reporting of the true prevalence of these diseases. Specific questions to obtain prospective information would provide useful information in monitoring trends in these patients in Australia and New Zealand and could be fed back to units as part of the ANZDATA annual report.
2. In those patients selected for transplantation, outcome data should be collected in a prospective fashion; preferably in the setting of a clinical trial.

## **CONFLICT OF INTEREST**

David Gracey has no conflict of interest according to the conflict of interest statement set down by KHA-CARI Guidelines

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## APPENDICES

Table1 . Summary of included studies

Study ID	Study type	Setting	N	Participant characteristics	Outcomes measured	Main Findings	Comments
<b>HIV</b>							
Qiu et al 2006 [11]	Retrospective registry data (UNOS)	US	38	Kidney transplant recipients	Graft survival Patient survival	Graft survival was higher among HIV-positive patients (76.1% vs. 65.1% at 5 yrs, P=0.21) Patient survival was higher among HIV-positive patients (91.3% vs 87.3% at 5 yrs, P=0.72)	
Carter et al 2006 [12]	Prospective study of consecutive patients	US	20	HIV-infected kidney recipients (receiving/not receiving thymoglobulin)	CD4+T cell count Infection Rejection reversal	Mean CD4+T: remained stable in patients who did not receive thymoglobulin, suppressed in those who received thymoglobulin. Opportunistic infections were suppressed. Rejection reversal occurred in 6/7 patients receiving thymoglobulin.	
Rodriguez et al 2003 [14]	Retrospective analysis	US	115	HIV-infected patients on chronic dialysis	Survival	Survival during HAART was 16.1 mo vs 9.4 mo	
Ortiz et al 1988 [15]	Prospective follow up	US	51	20 chronic HD patients with superimposed HIV infection, 31 HIV-associated nephropathy requiring chronic HD	Survival	17 patients who developed AIDS died after a mean of 93 +/- 32 days on HD. 12 asymptomatic HIV carriers were alive after a mean follow-up on chronic HD of 488 +/- 75 days. 5 five hemodialyzed patients with ARC were alive after 564 +/- 191 days.	
Abbot et al 2004 [17]	Retrospective cohort study	US	27851	Deceased donor kidney transplant recipients	Mortality Graft loss	HIV-infected recipients had improved survival compared with HIV-uninfected recipients (adjusted HR, 0.36; 95% CI, 0.05 to 2.53; P = 0.31)	
Roland et al 2008 [19]	Prospective series	US	18	HIV-infected Kidney transplant recipients	1-year survival 3-year survival	Patient survival: 94% kidney graft survival 83%	

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<b>Study ID</b>	<b>Study type</b>	<b>Setting</b>	<b>N</b>	<b>Participant characteristics</b>	<b>Outcomes measured</b>	<b>Main Findings</b>	<b>Comments</b>
Tan et al 2004 [20]	Case series	US	4	HIV+ kidney transplant recipients (from deceased donors)	Graft function Graft dysfunction Rejection Infectious complications Mortality	Good graft function (n=1), graft dysfunction (n=1), rejection (n=3), infections complications (n=1), mortality (n=0)	
Kumar et al 2005 [21]	Prospective study	US	40	HIV positive dialysis patients who received a kidney transplant 2001-2004	Rejection Survival	Patient survival 85% (1yr), 82% (2yr) Graft survival 75% (1yr), 71% (2yr)	
Trullas et al 2007 [22]	Prospective follow up of consecutive patients	Spain	3	Consecutive HIV positive kidney transplant recipients	Nadir Lymphocytopenia CD4+ T cell	Lymphocytopenia CD4+ T cell (n=2) Opportunistic infection (n=0) Bacterial infection (n=1)	
Gruber et al 2008 [23]	Case series	US	8	HIV positive primary kidney transplant recipients	Patient survival Graft survival Diabetes Infections Malignancy Progression of Hepatitis C	Patient survival 100%, graft survival 88%. No patients developed diabetes, infections, malignancy, progression of hep V virus related liver disease.	
Stock et al 2010 [24]	Prospective study	US	150	HIV positive kidney transplant recipients with CD4+ T-cell counts $\geq$ 200/ml, undetectable HIV-1 RNA and treated with stable antiretroviral regimen.	Patient survival Graft survival Acute rejection Opportunistic complications CD4+ T cell HIV-1 RNA	Follow up median 1.7 years. Patient survival at 1 year was 94.6% (95%CI 88.9-97.4) and at 3 years 88.2% (95% CI 78.3-93.8). Graft survival at 1 year was 90.4% (95%CI 83.9-94.3) and at 3 years 73.7% (95%CI 61.9-82.4). Rates fall between rates for all SRTR patients and those aged $\geq$ 65 years. Cumulative incidence of rejection was 31% (95%CI 24-40) estimated as 2 to 3 times higher than non HIV recipients. The percentage of CD4+ T cell counts did not change significantly ( $p=0.66$ ) over time.	
<b>HBV</b>							

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<b>Study ID</b>	<b>Study type</b>	<b>Setting</b>	<b>N</b>	<b>Participant characteristics</b>	<b>Outcomes measured</b>	<b>Main Findings</b>	<b>Comments</b>
Fabrizi et al (2005) [35]	Systematic review of retrospective cohort studies	Europe, Asia, South America	6 studies (6050 participants)	Kidney transplant recipients where information on HBsAg seropositivity was registered at the time of enrolment.	Patient survival Graft survival	Relative risk of all-cause mortality in HBsAg+ compared to HBsAg- patients 2.49 (95% CI:1.64-3.78). Relative risk of graft loss 1.44 (95% CI:1.02-2.04).	
<b>HCV Refer to KDIGO Tables 22 and 23</b>							
Kamar et al 2005 [46]	Retrospective study	US	51	Anti-HCV positive RNA positive kidney transplant recipients	Liver fibrosis progression	Liver fibrosis stabilised (n=21) Progressing liver fibrosis (n=21) Regression in liver fibrosis (n=10)	
Bouthot et al 1997 [47]	Prospective follow up study	US	103	23 anti-HCV-positive recipients, 80 anti-HCV-negative kidney recipients from anti-HCV-negative donors	Patient survival Graft survival	Compared with recipients without anti-HCV before Tx, graft loss among recipients with anti-HCV before transplantation was RR 1.30 (0.66-2.58), death RR 2.60 (1.15-5.90), death due to sepsis RR 6.30 (1.99-20). Compared with recipients of organs from anti-HCV-negative donors, graft loss among recipients of organs from anti-HCV-positive donors was RR 0.95 (0.54-1.67), death was RR 1.00 (0.49-2.02).	

Tables 22 and 23 reproduced from KDIGO (2008) [1]

**Table 22 | Summary table of patient mortality in HCV-positive kidney transplant recipients vs wait-listed HCV-positive hemodialysis patients<sup>a</sup>**

Author (year), country, study design	N	Test determining HCV status	Mean follow-up (months)	Outcome <sup>b</sup> Mortality
Pereira (1998), <sup>110</sup> United States, Retrospective	111 HCV+ kidney recipients 112 HCV+ patients on waiting list	EIA 3	73 (median)	Transplant vs dialysis <sup>c</sup> Adjusted RR of mortality <sup>d</sup> 0-3 months post-transplant: ~ 4.8 (significant) 4-6 months post-transplant: ~ 1.8 (NS) 7-47 months post-transplant: ~ 0.3 (significant) ≥ 48 months post-transplant: ~ 0.8 (NS)
Bloom (2005), <sup>253</sup> United States, Retrospective	138 HCV+ kidney recipients 177 HCV+ patients on waiting list	EIA 2 or EIA 3	48 (median)	Transplant vs nontransplanted: Actuarial mortality: ~ 20 vs ~ 50% (P=0.003)
Knoll (1997), <sup>254</sup> United States, Retrospective	33 HCV+ kidney recipients 25 HCV+ patients on waiting list	EIA 1 or EIA 2	39 35	Transplant vs dialysis <sup>e</sup> : Actuarial mortality: ~ 15 vs ~ 30% (P=0.04)

EIA, enzyme immunoassay; HD, hemodialysis; NA, not applicable; ND, not documented; NS: not significant; RR, relative risk.

<sup>a</sup>Nonsystematic review. No grading.

<sup>b</sup>No data provided on graft survival in these articles.

<sup>c</sup>All-cause mortality figures are for all transplant recipients vs dialysis, but point estimates for HCV-positive and HCV-negative transplant recipients were similar (see Figure 2 in text).

<sup>d</sup>Estimated from Figure 2 in text.

<sup>e</sup>Results approximate because extrapolated from Figure 1 in text. Eighteen HCV-positive patients who were not transplant candidates were also studied and had a 62% mortality rate in 29 months of follow-up.

## KDIGO References

### Table 22

Pereira (1998) [53]

Bloom (2005) [54]

Knoll (1997) [55]

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Table 23 | Summary table of adjusted mortality and graft loss in HCV-positive vs HCV-negative kidney transplant recipients<sup>a</sup>

Author (year), country, study design	N	Test determining HCV status	Mean follow-up (months)	Outcomes	
				Risk-adjusted patient mortality	Risk-adjusted graft loss
Meier-Kriesche (2001), <sup>350</sup> United States Retrospective	535 HCV+ 73 172 HCV–	EIA (unspecified)	ND <sup>b</sup>	HCV+ vs HCV– Adjusted mortality per 1000 patients: 35.7 vs 44.6 (P<0.01) ↓	ND
Abbott (2003), <sup>320</sup> United States Retrospective	2525 HCV+ <sup>c</sup> 34 431 HCV–	EIA (presumed)	33	HCV+ vs HCV– Adjusted HR of mortality: 1.34 (1.04–1.74) ↑	HCV+ vs HCV– Adjusted HR of graft loss: 0.85 (0.52–1.39) ↓
Batty (2001), <sup>261</sup> United States Retrospective	1624 HCV+ 27 068 HCV–	EIA (presumed)	ND <sup>d</sup>	HCV+ vs HCV– Adjusted HR for mortality: 1.23 (1.01–1.49) ↑	ND
Morales (2004), <sup>120</sup> Spain Retrospective	488 HCV+ 2877 HCV–	EIA 1, EIA 2, or EIA 3	ND	HCV+ vs HCV– Adjusted RR of mortality: 1.50 (1.12–2.02) ↑	HCV+ vs HCV– Adjusted RR of graft loss: 1.53 (1.17–2.00) ↑
Bruchfeld (2004), <sup>115</sup> Sweden Retrospective	51 HCV+ 520 HCV– <sup>e</sup>	EIA 1, EIA 2, or EIA 3 PCR <sup>f</sup>	ND <sup>f</sup>	HCV+ vs HCV– Adjusted RR of mortality: 2.23 (1.48–3.34) ↑	HCV+ vs HCV– Adjusted RR of graft loss: 1.96 (1.37–2.79) ↑
Legendre (1998), <sup>263</sup> France Retrospective	112 HCV+ 387 HCV–	EIA 2	79 81	HCV+ vs HCV– Adjusted OR of mortality: 2.8 (1.4–5.7) ↑	ND
Forman (2004), <sup>116</sup> United States Retrospective	26 HCV+ 328 HCV–	EIA (unspecified)	28 (median)	ND	HCV+ vs HCV– Adjusted HR of graft loss: 2.00 (0.73–5.46) <sup>g</sup> ↑
Gentil (1999), <sup>262</sup> Spain Retrospective	85 HCV+ 235 HCV–	EIA 1 or EIA 2	63 57	HCV+ vs HCV– Adjusted RR of mortality: 3.1 (1.2–7.8) <sup>h</sup> ↑	HCV+ vs HCV– Adjusted RR of graft loss: 3.0 (1.8–5.0) <sup>h</sup> ↑
Lin (2004), <sup>329</sup> Taiwan Retrospective	129 HCV+ 170 HCV–	EIA 1, EIA 2, or EIA 3	67	HCV+ vs HCV– Adjusted RR of mortality: 0.30 (0.13–0.65) ↓	HCV+ vs HCV– Adjusted RR of graft loss: 0.81 (0.48–1.35) ↓
Mahmoud (2004), <sup>292</sup> Egypt Prospective	87 HCV+ 46 HCV–	RT-PCR (Amplicor)	94 98	HCV+ vs HCV– Adjusted OR of mortality: 0.50 (0.1–1.9) <sup>i</sup> ↓	HCV+ vs HCV– Adjusted OR of graft loss: 0.50 (0.3–1.2) <sup>j</sup> ↓

EIA, enzyme immunoassay; HD, hemodialysis; HR, hazard ratio; KTR, kidney transplant recipient; NA, not applicable; ND, not documented; NS: not significant; OR, odds ratio; RR, relative risk; RT-PCR, reverse transcription-polymerase chain reaction.

↑, positive association—increase in death or graft loss (not statistically significant); ↓, negative association—decrease in death or graft loss (not statistically significant); ↑ and ↓, statistically significant association (P<0.05).

<sup>a</sup>Non-systematic review. No grading.

<sup>b</sup>Survival curves contain data up to 8 years.

<sup>c</sup>HCV+ recipients (23%) received HCV+ kidney, 0.8% of HCV– recipients received HCV+ kidneys.

<sup>d</sup>Survival curves contain data up to 3 years.

<sup>e</sup>Six patients were EIA-positive but persistently RNA-negative. They were classified as HCV-negative.

<sup>f</sup>Survival curves contain data up to 13 years.

<sup>g</sup>In multivariable models, the following factors had statistically significantly increased adjusted HR for graft loss: panel-reactive antibody > 20%, HLA mismatch ≥ 5, post-transplant delayed graft function, and acute humoral rejection.

<sup>h</sup>Text inconclusive of directionality of adjusted RR but reported values are consistent with the directionality of unadjusted risks.

<sup>i</sup>HCV RNA-positive patients with elevated ALT had OR of mortality: 3.7 (1.0–13.7).

<sup>j</sup>HCV RNA-positive patients with elevated ALT had OR of graft loss: 3.0 (1.4–6.7).

**KDIGO References**

**Table 23**

Meier-Kriesche (2001) [56]  
Abbott (2003) [57]  
Batty (2001) [58]  
Morales (2004) [59]  
Bruchfeld (2004) [60]  
Legendre (1998) [61]  
Forman (2004) [62]  
Gentil (1999) [63]  
Lin (2004) [64]  
Mahmoud (2004) [65]

**Table 2. Evidence Profile – Recipients Assessment for Transplantation - HIV**

Quality Assessment						Summary of findings					Importance
No. of studies and design	Study Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of patients <sup>b</sup>		Effect		Quality	
						Kidney Transplant Recipients HIV+	Control (HIV-)	Relative (95% CI)	Absolute		
<b>Outcome: Patient survival</b>											
Retrospective Registry [11]	Serious limitation (1)			Serious limitation (2)		38	38	NA	HIV+ 91.3% at 5 years	Very low	Critical
									HIV- 87.3% at 5 years (p=0.21)		
Retrospective Registry [17]	Serious limitation (1)			Serious limitation (3)		2 deaths / 47 (4.3%) by 3 years.	3569 (deaths) / 27,851 (12.8%) by 3 years.	Adjusted HR 0.36 (CI 0.05-2.53)	Based on 95% CI from 120 fewer to 200 more per 1,000)	Very low	Critical
<b>Outcome: Graft survival</b>											
Retrospective Registry [11]	Serious limitation (1)			Serious limitation (2)		38	38	NA	HIV+ 76.1% at 5 years	Very low	Critical
									HIV- 65.1% at 5 years (p=0.21)		
Retrospective Registry [17]	Serious limitation (1)			Serious limitation (3)		3 graft failure / 47 (6.4)% by 3 years	5,467 graft failure / 27,851 (19.6)% by 3 years	NE	NE	Very low	Critical

NE – Not able to be estimated.

- (1) Limited evaluation of confounders
- (2) Small sample size
- (3) Small event rate with respect to HIV+. Very large confidence interval.
- (4) No controls, no evaluation of confounders.

**Table 3 - Evidence Profile – Recipients Assessment for Transplantation - HBV**

Quality Assessment						Summary of findings					Importance
No. of studies and design	Study Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of patients <sup>b</sup>		Effect		Quality	
						Kidney Transplant Recipients HCV+	Control HCV-	Relative (95% CI)	Absolute		
<b>Outcome: Patient Mortality</b>											
1 Systematic review [35]	Very serious limitations (1)		No limitations			79 (deaths) / 260 (30%)	345 (deaths) / 2425 (1.4%)	2.49 (95% CI 1.64-3.78)	212 more per 1000	Low	Critical
<b>Outcome: Graft loss</b>											
1 Systematic review [35]	Very serious limitations (1)		No limitations			71 (grafts lost) / 260 (27%)	724 (grafts lost) 2425 (30%)	1.44 (95% CI 1.02-2.04)	131 more per 1000	Low	Critical

(1) No adjustment for potential confounders have been made. Selection criteria unclear.

**Table 4. Evidence Profile – Recipients Assessment for Transplantation – HCV (not in KDIGO [1])**

Quality Assessment						Summary of findings					Importance
No. of studies and design	Study Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of patients <sup>b</sup>		Effect		Quality	
						Kidney Transplant Recipients HCV+	Control HCV-	Relative (95% CI)	Absolute		
<b>Outcome: Patient Mortality</b>											
1 Retrospective cohort [47]	Very serious limitations (1)	NA	No limitations	Serious limitation (2)		9 (deaths) / 22 (41%)	16 (deaths) / 78 (21%)	2.60 (95% CI 1.15-5.90)	328 more per 1000	Very low	Critical
<b>Outcome: Graft loss</b>											

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Quality Assessment						Summary of findings					Importance
						No. of patients <sup>b</sup>		Effect		Quality	
No. of studies and design	Study Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Kidney Transplant Recipients HCV+	Control HCV-	Relative (95% CI)	Absolute		
1 Retrospective cohort [47]	Very serious limitations (1)	NA	No limitations	Serious limitation (2)		12 (grafts lost) / 22 (55%)	34 (grafts lost) 79 (43%)	1.30 (95% CI 0.66-2.58)	Range from 146 fewer to 129 more per 1000	Very low	Critical

(1) No adjustment for potential confounders have been made. Selection criteria unclear.

(2) Small sample size and large confidence limits