HBV, HCV, HIV and Kidney Transplantation

Simin Goral MD
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania
Objectives

• Prevalence of hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV) in ESRD population
• Transplant evaluation of patients with these viral infections
• Kidney transplantation in patients with HBV, HCV or HIV
  • Immunosuppression
  • Outcomes
  • New developments
Case #1

- 54 year old AA male, on dialysis since 2007, blood group O
- Has polycystic kidney disease, HIV positive—diagnosed in 1993, on antivirals, hepatitis B surface antigen positive
- Came in for kidney transplant evaluation
Case #2

- 60 yo AA male; on dialysis since 1/2015; blood group B
- Has history of diabetes, hypertension, hepatitis c-was treated; now has no HCV viral load
- Came in for kidney transplant evaluation
HBV, HCV, HIV Infections

• Pre-existing HBV, HCV or HIV infections: were relative contraindications to kidney transplant in the past

• Concerns:
  • Effects of immunosuppressive drugs on viral replication, leading to acceleration of liver injury and progression to hepatocellular failure/death
  • Development of *de novo* GN in the graft
Hepatitis B (HBV)

• The prevalence of chronic HBV infection: differs between regions
  • Low rates (≤2%) in Western Europe and the U.S
  • Intermediate rates (2–8%) in Mediterranean countries and Japan
  • High rates (8–20%) in Southeast Asia and Sub-Saharan Africa

• Successful vaccination in CKD/ESRD patients, improved infection control in dialysis units, and widespread use of EPO rather than transfusions for anemia
HBV Serologic Markers

- Positive HbsAg/HBV DNA/HbeAg: active infection
- Positive HbcAb IgM: a marker of acute or reactivated infection
- Positive HbsAb: immunity (anti-Hbs>10 IU/mL protective)
- Positive HbcAb: in the absence of HBsAg, could be a false positive result, past exposure with resolved infection, or rarely chronic HBV infection with detectable HBV DNA

Huprikar S, et al. AJT 2015
Transplant Evaluation of Patients with HBV

- All candidates should be screened
- Obtain serologies and HBV viral load
- All candidates who are HbsAg positive: refer to Hepatology
  - Most patients require a liver biopsy
  - To make sure that they do not have cirrhosis and portal hypertension
  - Also the need for treatment
Impact of Pre-existing HBV Infection on Outcomes

- 1346 HBsAg+ recipients from UNOS database 2001-2007
- 5 yr death-censored graft survival 85.2% and patient survival 85.3% in HbsAg+; no significant difference from HBV- patients
- 5-yr cumulative incidence of hepatic failure higher in HBV+ recipients (1.3% vs 0.2%; $P < 0.001$)-still low, 5x risk of severe liver disease in HBV+ recipients

Reddy P, et al. CJASN 2011
Effective HBV therapies have improved outcomes significantly

- **Lamivudine** was the primary antiviral agent used for the treatment of chronic HBV both before and after transplantation.

- **New agents**: potent oral nucleoside analogs with a high genetic barrier to resistance such as entecavir and tenofovir (very low resistance rates (<1%) in treatment naive patients).

_Huprikar S, et al. AJT 2015_
# Antiviral Treatments for HBV Infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anti-viral potency</th>
<th>Barrier to resistance</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir</td>
<td>+</td>
<td>++</td>
<td>Nephrotoxicity, diabetes insipidus, Fanconi syndrome</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>++</td>
<td>+</td>
<td>Lactic acidosis, pancreatitis</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>++</td>
<td>+</td>
<td>Lactic acidosis, anemia, leukopenia</td>
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<tr>
<td>Telbivudine</td>
<td>+++</td>
<td>+</td>
<td>Neuropathy, myopathy, elevated creatinine kinase</td>
</tr>
<tr>
<td>Entecavir</td>
<td>+++</td>
<td>+++</td>
<td>Lactic acidosis, transaminitis</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>+++</td>
<td>+++</td>
<td>Nephrotoxicity, Fanconi syndrome, lactic acidosis, osteomalacia</td>
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Use of HBV-positive Donors (HbsAg negative and anti-HbcAb positive)


- Anti-HbcAb positive kidneys resulted in a higher incidence of anti-Hbc antibody seroconversion; was not associated with a higher incidence of HbsAg detection.

Fong TL, et al. Transplantation 2002
HBV vaccination is recommended for all non-immune (anti-Hbs antibody negative) transplant candidates and recipients

HBV DNA with or without HbsAg should be monitored every 3 months for 1 year posttransplant

HBIG is not recommended

Huprikar S, et al. AJT 2015
Hepatitis C (HCV)

- Estimated to affect approximately 170 million individuals worldwide
- Prevalence of HCV in patients with ESRD (5% and 60%) far exceeds that of the general population (~1% prevalence in the US)
- HCV-infected patients with CKD has an increased mortality and an accelerated rate of progression to ESRD
- Liver failure and hepatocellular carcinoma are the major long-term complications in chronic HCV-infected patients
- Patients co-infected with HIV have an increased mortality and overall worse prognosis

HCV and Kidney Transplant

• KDIGO (2008): all kidney transplant candidates should be tested for HCV infection via antibody screening or nucleic acid testing (NAT)

• All patients who are HCV NAT positive should be referred to Hepatology for liver biopsy to assess the degree of hepatic disease severity prior to transplantation

• Updates are expected

Transplant Evaluation of Patients with HCV

- Liver enzymes and HCV viral load correlate poorly with disease activity and liver fibrosis in advanced CKD
- Liver biopsy remains the “gold standard”
- Transient elastography (FibroScan) is emerging as a highly reproducible noninvasive technique—but liver stiffness is affected by central venous pressure
Patients with HCV infection on a waiting list had **2.19 times higher** risk for death than those patients who received kidney transplantation - **survival benefit**

Transplant provides a survival benefit for HCV+ patients

Benefit of kidney transplantation - approx **55% lower risk of death at 5 years**

Waiting list group had **higher risk of cardiovascular diseases**

Survival advantage particularly in HCV patients **aged 45 years or older**

• 18 observational studies; 133,530 renal transplant recipients
• **Increased all-cause mortality** mostly due to cardiovascular disease
• HCV+ patient outcomes are inferior to HCV-
• Meta-regression showed that living donor rate had a favorable influence on patient (P = 0.031) and graft survival (P = 0.01), whilst diabetes having a detrimental role on patient survival (P = 0.001)

*Fabrizi F, et al. J Viral Hepatitis 2014*
• The link between HCV and **lower graft survival after kidney transplant** was demonstrated irrespective of reference year, country of origin or size of the study group

• **Causes of graft loss**: increased risk of new onset diabetes after transplant, recurrence of HCV-associated glomerulonephritis and chronic rejection/transplant glomerulopathy/TMA

*Fabrizi F, et al. J Viral Hepatitis 2014*
Immunosuppression in Patients with HCV

- UNOS database; 3708 HCV+ and 75,629 HCV- kidney transplant recipients
- Increased mortality risk for HCV+ kidney transplant recipients compared with HCV- recipients, particularly among younger age groups
- With HCV positive serology, the use of induction therapy was not associated with an increased mortality risk

A lower mortality risk with induction was observed beyond the first 2 years after tx.

The choice of CNI (CsA or Tac) and use vs nonuse of steroids had no effect on patient mortality.

The use of MMF (yes vs no) was associated with a significantly reduced mortality rate.

Use of HCV-positive Kidneys

- HCV+ organs to HCV+ recipients
- Overall shortage of suitable donor kidneys/long waiting times; not every center accepts these kidneys
- Usually limited to recipients who are viremic with genotype 1
- Risk of superinfection with other HCV genotypes
- With new direct-acting antivirals to cure HCV, no need to limit to genotype 1 recipients
• 162 HCVR+ received a kidney from HCVD+ (group 1) and 306 from HCVD− (group 2)

• Similar patient survival: Five- and 10-year patient survival was 84.8% and 72.7% in group 1 vs. 86.6% and 76.5% in group 2 (p = 0.250)

• Decreased graft survival: Five- and 10-year graft survival was 58.9% and 34.4% versus 65.5% and 47.6% respectively (p = 0.006)

• Decompensated chronic liver disease was similar: 10.3% versus 6.2%.

Morales JM, et al. AJT 2010
Treatment of HCV

- KDIGO guidelines: treatment of HCV in all kidney transplant candidates-interferon based; low response rate and poor tolerability
- Treatment with interferon after transplant is not recommended-increased rejection risk
- New interferon-free direct acting antiviral (DAA) regimens-cure rates up to 90% and efficacious posttransplant as well

Fig 1. Hepatitis C Direct-Acting Antiviral.


http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0158431
DAA Agents for Treatment of HCV

DAA-Based Regimens in HCV

**Treat pretransplant**
- Can remain active on the waitlist during therapy
- Cure of HCV is likely
- Prevent disease transmission
- Avoids drug-drug interactions with immunos
- Possible decreased risk:
  - Progressive liver disease
  - Posttransplant GN
  - New onset diabetes posttransplant

**Do not treat pretransplant**
- Efficacious and safe posttransplant
- Potential drug-drug interactions
- Cure eliminates HCV+ organ
  - Longer waiting time
  - Increased kidney discard rate

*Sawinski et al. Transplantation 2015*
All patients cleared the virus quickly while on therapy, and 100% have achieved a sustained virologic response at 12 weeks after completion of DAA therapy.

Most commonly used regimen: sofosbuvir 400 mg + simeprevir 150 mg daily.

DAAs Clear HCV Viremia Posttransplant

- 20 consecutive kidney recipients
- 88% were infected with genotype 1; 50% had biopsy-proven advanced hepatic fibrosis on most recent liver biopsy
- 60% had failed treatment pretransplant with interferon-based therapy

Sawinski, et al. AJT 2016
Use of DAAs Posttransplant

- DAA-immunosuppression drug-drug interactions are very important
- CNI levels have been shown to fluctuate during and even after DAA treatment is completed
- Need for careful monitoring of kidney function and CNI drug levels both during and after therapy
- Combined efforts by hepatologists and transplant nephrologists

HIV and Kidney Transplantation

- With HAART use, decline in HIV-related deaths; number of patients living with HIV increased
- HIV is the third-leading cause of ESRD in African Americans after diabetes and hypertension
- Kidney transplantation is now offered as an acceptable treatment option for HIV+ ESRD patients
- High incidence of acute rejection
- Increased risk of delayed graft function
Evaluation of HIV Positive Candidates

- All patients are required to have:
  - CD4 count >200/mm³
  - An undetectable HIV viral load on stable antiviral therapy for at least 6 months prior to transplant
  - No significant opportunistic infections
  - Evaluation by Transplant Infectious Diseases
HIV and Kidney Transplantation

Locke J, et al. JASN 2015
**Patient Survival-HIV+ Patients**
(SRTR; 2002–2011; 510 adults, median follow-up: 3.8 years)

- **PS:** similar for HIV-monoinfected recipients and HIV negative/HCV negative controls both at 5 years and 10 years
- **HIV/HCV coinfected recipients had worse PS** compared with HIV-negative/HCV positive controls

_Locke J, et al. JASN 2015_
Graft Survival-HIV+ Patients
(SRTR; 2002–2011; 510 adults, median follow-up: 3.8 years)

- GS: similar for HIV-monoinfected recipients and HIV negative/HCV negative controls both at 5 years and 10 years
- HIV/HCV coinfected recipients had worse GS compared with HIV-negative/HCV positive controls

Locke J, et al. JASN 2015
HIV-positive patients had a **1.77-fold higher risk of AR** at 1 year compared with their HIV-negative counterparts (15% vs 8%).

Among HIV-positive and HIV-negative patients receiving ATG induction therapy, the risk of AR was 1.16 and was not statistically different.

HIV-positive patients that received **ATG induction had a 2.6-fold or 61% lower risk of AR at 1 year** compared with no induction therapy.

Sirolimus-based therapy had a **2.2-fold higher risk of AR at 1 year**

*Locke J, et al. Transplantation 2014*
• 830 HIV+ kidney transplant recipients (from 2000-2014)
• HIV+ recipients who received induction spent fewer days in the hospital, had lower rates of DGF, less graft loss, lower rates of AR (with ATG induction), and a trend toward lower mortality
• Induction therapy was not associated with increased infections

HIV Medications and Immunosuppression

- Profound drug-drug interactions, especially with protease inhibitors
- Frequent drug level monitoring of CNIs
- New integrase inhibitors, CCR5-antagonists and fusion inhibitors cause significantly less pharmacokinetic interactions
- Must work closely with an Transplant Infectious Diseases expert
HIV and Kidney Transplantation

• Prospective, nonrandomized study of kidney transplantation in 27 HIV-infected patients (CD4 count > 200 and undetectable HIV RNA level)-all on antivirals; received HIV positive kidneys - results at 5 years

• Patient survival: 84% at 1 year, 84% at 3 years, and 74% at 5 years; graft survival: 93%, 84%, and 84%

• Rejection rates were 8% at 1 year and 22% at 3 years.

• HIV infection remained well controlled, with undetectable virus in blood after the transplantation

Muller E, et al. NEJM 2015
Kidney as a Reservoir for HIV after Transplantation

- Protocol biopsies from 19 recipients with HIV-1 who did not have detectable levels of plasma HIV-1 RNA at transplantation.
- HIV-1 infected the kidney allograft in 68% of these patients; HIV-1 infection was detected in either podocytes predominately (38% of recipients) or tubular cells only (62% of recipients).
- HIV-1 can re-infected kidney allografts after transplantation despite undetectable viremia, and this infection might influence graft outcome.
- Close monitoring of proteinuria is needed after transplantation.

HIV Organ Policy Equity Act (HOPE Act)

- Enacted on November 21, 2013
- Allows for the development and publication of criteria for research relating to transplantation of organs from donors infected with HIV into individuals who are infected with HIV
Summary

• HBV+ recipient outcomes have improved significantly with vaccination and antiviral therapy
• HbcAb positive organs can be used safely for most patients
• Treatment of HCV with interferon-free regimens is now possible; long-term studies needed
• HIV+ kidney transplant recipients have excellent patient and allograft survival