HIV and Liver Transplantation: challenges and opportunities

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Key messages

- Liver transplant patient criteria
- Describe pre/intra/post transplant process
- King’s experience in liver transplantation in HIV +ve patients
- Drugs used in liver transplant
- Drug-drug interactions with ARV’s
- Outcomes
What are the indications for consideration of liver transplantation?
Indications for Transplantation

- Acute liver failure
- Decompensated liver disease with;
  - ascites
  - encephalopathy (having excluded HIV related dementia)
  - problematic varices
  - poor synthetic function e.g. albumin < 30g/l, INR >1.5 and elevated serum bilirubin e.g. > 50umol/l.
- Hepatocellular carcinoma meeting Milan criteria
- Prognosis (excluding liver disease) of 50% survival for 5 years

HIV specific parameters for liver transplantation

- CD4 counts > 200 cells/ul or > 100 cells/ul in the presence of portal hypertension
- Absence of HIV viraemia
- Absence of AIDs defining illness after immune reconstitution
- Antiretroviral therapeutic options available if HIV disease reactivates

Absolute contraindications to liver transplantation

- Alcohol-related liver disease without total abstinence for six months
- Currently injecting intravenous drug use
- Cholangiocarcinoma
- Extrahepatic malignancy
- Uncontrolled extrahepatic sepsis e.g. endocarditis
- Total thrombosis of the porto-mesenteric system
- Severe pulmonary hypertension (mean pulmonary pressure > 50-55mmHg)

Transplantation in HIV+ve individuals

- **Pre-HAART**
  - Poor prognosis – opportunistic infections, AIDs
  - Transplantation outcomes were poor

- **1996 – HAART**
  - Chronic kidney, liver, cardiac disease leading cause of mortality in HIV-infected individuals
  - Advanced liver disease is the leading cause of death in HIV-HCV and HIV-HBV co-infected patients.

KCH liver transplant patients

24 HIV+: 21♂ 3♀

[HIV+/HCV]
  n = 11

[HIV+/HBV]
  n = 6

[HIV+/Other] *
  n = 7
  * Other = HCC (1), HAT (2), ALD (1), SALF (1), HPS (1), NANB (1)
Concerns?

- Accelerated HIV progression; immunosuppression in an immuno-suppressed individual – risk of disease progression, ↓CD4 and/or ↑VL?

- Increased opportunistic infections?

- Outcomes – prognosis 50% survival for 5 years?

- Drug interactions
Immunosuppression

- **Primary HIV infection**
  - immune activation
  - HIV infects both resting and activated CD4 T cells but replicates only in activated CD4 T-cells

- **Chronic HIV infection**
  - immune activation persists
  - continuous production of pro-inflammatory cytokines (IL2, IL6, TNF)
  - increased turnover of B and T cells, activation of T cells
Immunosuppression in HIV+ve individuals

- Ciclosporin (CsA)
  - Inhibits T-cell activation by interfering with IL2 synthesis
  - CsA binds to cyclophilin (CypA)
  - Complex CsA-CypA binds calcineurin and inactivates a phosphate activity necessary for the dephosphorylation and activation of activated T-cell
  - Cyclophilin is required for HIV viral replication
  - CsA can modulate HIV activity by forming a complex in the virion core with HIV-Gag protein, blocking nuclear import of HIV-DNA in activated T-cells
  - ? CsA confers immunological benefits
Immunosuppressant options

- Calcineurin inhibitors – Tacrolimus, Ciclosporin
- Antimetabolites – Azathioprine, Mycophenolate
- TOR inhibitor – Sirolimus
- Steroids
- Monoclonal antibodies - Daclizumab, Basilixumab, Campath
- Polyclonal antibodies – Anti-thymocyte-globulin (ATG)
Tacrolimus versus micro emulsified ciclosporin in liver transplantation: the TMC randomised controlled trial


Primary outcome (death, retransplantation, or treatment failure for immunological reasons) was reached in 21% of patients in the tacrolimus group versus 32% in the micro-emulsified ciclosporin group (p = 0.001)

Tacrolimus should be the first choice of calcineurin inhibitor for patients receiving their first liver graft
Standard Immunosuppression post LT at KCH

1. Tacrolimus 1-3mg BD to achieve 12 hour trough level of 8-12mg/L
2. Methylprednisolone 1g IV intra-op
3. Methylprednisolone 16mg IV OD or Prednisolone 20mg PO OM* tapered to discontinuation by week 12
4. Daclizumab (IL2 blocker) 1mg/kg IV D0 and D7 if eGFR < 50mls/min pre-transplant

- Steroid taper may not be appropriate depending on indication for transplant, episodes of rejection, other immunosuppressants, age of recipient.
Tacrolimus

- Mechanism of action
  - Calcineurin inhibitor
  - Tacrolimus binds to cytosolic protein (FKBP12). The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin
  - This leads to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby suppressing:
    - T-cell activation and T-helper cell dependent B-cell proliferation
    - Formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.
- Available formulations: capsules, liquid, IV, prolonged-release capsule (Advagraf)
- Side-effect: ↑BP, ↑BM’s, renal dysfunction, ↓Mg2+, CNS, ileus
PI’s and Tacrolimus

- > 90% metabolised by CYP P450-3A4
- Inhibitor of P-glycoprotein
- Significant interactions with;
  - Protease inhibitors
    - Literature suggests 10-50 fold dose reduction in tacrolimus to maintain therapeutic levels in LT recipients\(^1\)
    - KCH experience; tacrolimus dose = 0.315mg/day (range 0.5mg -1mg every 14d)
  - Raltegravir does not appear to interact with tacrolimus
    - Not metabolised by CYP P450
    - Major mechanism of clearance is UGT1A1-mediated glucuronidation

<table>
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<th>ID</th>
<th>LT indication</th>
<th>Race</th>
<th>PI</th>
<th>Other ARV</th>
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<td>1</td>
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<td>SALF 2°EFV</td>
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<td>Raltegravir</td>
<td>Kivexa Entecavir</td>
<td>3mg/d</td>
<td>MMF 1g BD</td>
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</table>
NNRTI’s and Tacrolimus

- **Effavirenz**
  - Induces CYP 3A4
  - Inhibits CYP 2C9, 2C19, and 3A4
  - Reduces tacrolimus levels
  - KCH experience (n = 7);
    - tacrolimus dose = 7mg/d (range 0.5 – 12mg/d)

- **Nevirapine**
  - Induces CYP 3A4, and 2B6
  - Reduces tacrolimus levels
  - KCH experience (n = 2);
    - tacrolimus dose = 4mg/d (range 2-6mg/d)
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<tr>
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<td>Race</td>
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<td>Trizivir, TDF</td>
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Tacrolimus doses used with HAART

- Protease inhibitors
  - 0.315mg/d
- NNRTI’s
  - 6.4mg/d
- NRTI’s
  - 8.2mg/d
- Non-HAART
  - 7mg/d
Management of Tacrolimus interactions

- How does management differ from kidney transplant
  - Pre-transplant liver dysfunction – PK studies not possible
  - Living-donor transplant numbers are small – additional drug toxicity whilst on waiting list
- Tacrolimus 1-2mg PO BD for 2 doses
- Daily levels to achieve target trough tacrolimus level of 8-12mg/L
- Redose with 0.5 –1mg at intervals depending on daily monitoring and target trough levels.
- Administration post-op: PO/SL.

- N.B Be aware of drug interactions when starting and stopping HAART
**Mycophenolate**

**Mechanism of action**
- Prodrug of mycophenolic acid (MPA)
- IMPDH (inosine monophosphate dehydrogenase) inhibitor
- MPA inhibits de novo synthesis of purines in T and B lymphocytes, thus prevents proliferation of T and B lymphocytes

**Side-effect profile**
- GI disturbance, bone marrow suppression

**Role in liver transplantation**
1. Boost current IS – add if > 1 episode of ACR
2. Renal sparing – add if eGFR < 50mls/min with CNI sparing

**Formulations**
- Tablets, capsules, liquid, IV
- Mycophenolic acid (Myfortic) - ? Reduced GI side-effects
Mycophenolate

Metabolised

- MMF hydolyzed to mycophenolic acid (MPA) in liver
- MPA, the active compound, is a substrate of glucuronyl transferase
- MPA metabolised in liver and intestine by enzyme UDP-glcuronosyltransferase, forming MPAG (inactive).
- MPAG excreted in urine and bile.
- Once excreted in bile, MPAG can be hydolyzed by bacterial glucuronidases and reabsorbed as MPA – enterohepatic recirculation.

Therapeutic Drug Monitoring (TDM)

- Current evidence in favour of monitoring is weak\(^1\)
- Many factors affecting MMF level – e.g. protein binding, renal failure, EHC

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MMF interactions with HAART

- **Protease inhibitors**
  - Ritonavir, Kaeltra, Nelfinavir; May ↓ MMF via GT induction
  - In a small case series (n=6) – no significant change in indinavir concentrations with MMF

- **NNRTI’s**
  - Nevirapine; In a small case series (n = 6), NVP clearance ↑ by 27% in the presence of MMF

- **NRTI’s**
  - Zidovudine – both are substrates of glucuronyl transferase; competitive inhibition may result in ↑ AZT or MPA

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1. Antiretroviral Interactions with Transplant Medications. Alice Tseng and Trish Marr, Toronto General Hospital. www.tthhivclinic.com (N.B. No longer available)
Management of MMF interactions with HAART

- Little known
- Role of TDM uncertain
- TDM of HAART if possible
- Monitor clinical response and indirect parameters – LFT’s, CD4, VL.
When to start HAART post LT?

Peri-operative management

- Risk of resistance – different t½ of anti-retrovirals

Standard

- Give pre-op, immediately post-op
- NBM – 0 days, E+D once ex-tubated
- Except Roux-en-Y – NBM 5d, medications administered with sips/NG

Fulminant hepatic failure or not on HAART

- Identify cause of liver failure
- Start as soon as possible once clinically stable
**OI prophylaxis; Standard protocol**

- **Fungal prophylaxis**
  - Fluconazole 50mg/d until prednisolone dose < 10mg/d
  - Increased 200mg/d if high-risk transplant (acute liver failure, LITU admission), biliary complications or to boost tacrolimus levels

- **CMV** prophylaxis for CMV mismatch recipients (D+/R-ve)
  - Valganciclovir 900mg/d for 90days, started D7 post LT
  - Ganciclovir 5mg/kg IV if NBM, absorption problems
  - Adjusted according to renal function

- **Toxoplasmosis**
  - Mismatch; Donor +ve/Recipient –ve
  - Co-trimoxazole 480mg/d for 6-12 weeks post LT

- **Hepatitis B**
  - Standard: HepBcAb +ve: Lamivudine 100mg/d life-long
  - HIV +ve: Adjust HAART to include HBV active ARV’s
Other prophylaxis

- **Gastric acid suppression**
  - PPI (omeprazole 20mg/d) until prednisolone dose < 7.5mg/d

- **Peri-operative surgical prophylaxis**
  - Tazocin/Meropenem and Vanc/Linezolid for pre and 24-48 hours post LT
  - Prolonged course, 5 days, in allograft dysfunction

- **Thromboprophylaxis**
  - Start once INR < 1.5, Plts > 50.
  - Heparin 5000iu SC BD
Monitoring

- Graft function
  - Daily LFT’s, US D0 +D5, CT, biopsy
- OI’s
  - Infection (bacterial + fungal d1-d14 post LT, > 14d post LT viral)
  - CMV DNA weekly, then as per symptoms
- Drug’s
  - Tacrolimus - levels 3 x week, BP, BM’s, renal
- Disease recurrence
  - HBV DNA, HCV RNA + biopsy at 1 year
- Long-term
  - Cardiovascular risk
  - Renal dysfunction
  - Cancer
Outcomes

- Incidence and treatment of acute rejection
- Long-term patient and graft survival
- Incidence of opportunistic infections – CD4 and VL
KCH outcomes; Rejection

- 46% patients had episodes of rejection
- 18 episodes of rejection in 11 patients
- Day post LT: 184

Treatment
- Nil (n = 2)
- Methylprednisolone 1g IV 3 dose (n = 10)
- MMF added (n = 2)
- Tacrolimus dose increased, prednisolone added (n = 1, AIH)
- Basiliximab 20mg IV (n = 1)
- Unknown (n = 2)

Options for treatment of rejection
1. Augment IS
2. Methylprednisolone 1g IV x 3 doses
3. IL2 blocker e.g. Daclizumab 1mg/kg IV D0 and D7
4. Polyclonal antibodies – ATG 2mg/kg/d IV, max cumulative dose of 21mg/kg. NB OI prophylaxis
Outcomes of all HIV positive Liver Transplant recipients.

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<th>Author, Year, Country</th>
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<td>69.8</td>
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<td>Rafecas, 2004, Spain</td>
<td>4</td>
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<td>Moreno, 2005, Spain</td>
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<td>Radecke, 2005, Germany</td>
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<td>Schreibman, 2007, USA</td>
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<td>Vennarecci, 2007, Italy</td>
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<td>Mindikogulu, 2008, USA</td>
<td>138</td>
<td>80</td>
<td>70</td>
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Outcomes; Mortality

KCH experience (n=24)

- Deceased (n=4)
- Time to death post LT: 1 day, 4mths, 5 mths, 122 mths
- Liver failure (n=2), acute cerebral bleed (n=2), sepsis/ aspergillosis (n=1)
## KCH Outcomes (n = 24): Sepsis

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<thead>
<tr>
<th>ID</th>
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<th>VL</th>
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<td>&lt;50</td>
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<td>-</td>
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<td>965</td>
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<td>Combivir</td>
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<td>CMV viraemia and pneumonitis</td>
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Outcomes; Disease recurrence
Liver Transplantation for HIV: Analysis of outcomes suggest HIV+/HCV co-infected patients have prohibitively poor survival at 5 years


†Department of Hepatology, St James’s Hospital, James’s Street, Dublin, Ireland; *Institute of Liver Studies, King’s College Hospital, Denmark Hill, London, UK

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Concerns?

- Outcome of recurrent HCV and timing of anti-HCV therapy\(^1\)
- Type of HAART in combination with immunosuppressive drugs
- Effect of newer immunosuppressive drugs, such as sirolimus/everolimus, or belatecept on HIV infection

1. BHIVA Guidelines for the management of co-infection with HIV-1 and chronic hepatitis B or C (2009). In consultation phase.
Summary

- No increase in HIV disease progression
- No increase incidence of opportunistic infections
- Outcomes – prognosis 50% survival for 5 years?
- Multidisciplinary approach – key role for pharmacists in the management of complex drug interactions
Further questions?

- Outcome of recurrent HCV and timing of anti-HCV therapy

- Effect of newer immunosuppressive drugs, such as sirolimus/everolimus, or belatecept on HIV infection
Questions?