Clinical Case Discussion:
DDIs in Transplantation

Saye Khoo, Neal Marshall, Sanjay Bhagani
Impact of highly active antiretroviral therapy on

- AIDS-related mortality
- incidence of HIV-related ESRD, and
- mortality in patients with HIV and ESRD

Cross sectional retrospective case control study (N = 2854)
age, sex matched HIV neg. controls (N = 8562)
HIV+ patients at all ages:
- ↑ prevalence of renal failure, bone fracture, diabetes, ≥ 2 conditions simultaneously

< 60 years old, HIV patients ↑ prevalence of CV disease, HTN than HIV neg controls

Guaraldi G et al. CID 2011; 53:1120
The patient

- **49yo, hetrosexual, black-African male**

- **HIV – positive 1991**
  - MAI (1994), Cryptosporidiosis (1994), recurrent HSV (aciclovir resistant)
  - CXR – scarring RUL ? Old TB (no history of treatment)
  - On ART since 1991, VL<50c/ml past 8 years
  - current CD4 500+ cells; nadir CD4 <50
The patient

Comorbidities

• Chronic HBV
  – HBsAg positive, cAb, eAb positive,
  – Hep eAg negative

• Fatty liver on US, splenomegaly

• Type II Diabetes (insulin controlled) 2004

• Hypertension

• Diarrhoea - normal OGD and colonoscopy Aug 2013
  – Up to 10x day without loperamide
  – Normal D2 biopsy
  – Stoll cultures negative including ova, cytata, parasites
## Extensive Antiretroviral Exposure

<table>
<thead>
<tr>
<th>Start</th>
<th>Stop</th>
<th>Regimen</th>
<th>Outcome</th>
<th>Actual</th>
<th>Anticipated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>1993</td>
<td>ZDV monotherapy</td>
<td>failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>1996</td>
<td>ddI monotherapy</td>
<td>failure</td>
<td></td>
<td></td>
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<tr>
<td>1996</td>
<td>1998</td>
<td>d4T + 3TC + IDV</td>
<td>VF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>1998</td>
<td>d4T + 3TC + ddI + HU + SQVr + EFV</td>
<td>VF, CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>2001</td>
<td>d4T + 3TC + ddI + HU + SQVr + NVP</td>
<td>VF</td>
<td>M184V,</td>
<td>K103N</td>
</tr>
<tr>
<td>2001</td>
<td>2002</td>
<td>d4T + 3TC + ddI + NVP + LPVr</td>
<td>VF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>2003</td>
<td>TDF + ddI + d4T</td>
<td>VF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>2004</td>
<td>TDF + ddI + LPV/SQV/r</td>
<td>VF</td>
<td>L90M,</td>
<td>I84V</td>
</tr>
<tr>
<td>2004</td>
<td>2004</td>
<td>TDF + ddI + d4T + EFV</td>
<td>VF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>2007</td>
<td>TDF + ddI + d4T + fAPVr</td>
<td>&lt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>2010</td>
<td>TDF + ATV/ fAPVr</td>
<td>&lt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td>DRVr (800/100)</td>
<td>&lt;50</td>
<td></td>
<td>X4 tropic</td>
</tr>
</tbody>
</table>
Clinical Progress

- treatment-experienced
- serial VF until bPI regimen in 2005
- virologically suppressed from 2005

CD4 (cells/mm³)


CD4

VL

HBV DNA negative

Viral Load

Clinical Progress
Multiple Co-morbidities, Renal Stress

- glomerulosclerosis
- mesangial expansion
- thickened basement membrane
- increased extracellular matrix

HIV

HIVAN

ARV

Diabetes

Chronic HBV

Hypertension

IDV, ATV, TDF

Metabolic syndrome

Renal Biopsy 2007

Diabetic Nephropathy
• Progressive renal impairment despite best efforts
• Endstage renal dysfunction due to diabetic nephropathy
• Required hemodialysis from 2012
What's his life expectancy?

Years of life remaining at 45-54 years, and 55-64 years (U.S.A).

Comparison of Persons with Selected Chronic Diseases
Renal transplantation vs waitlisted candidates on dialysis

Adjusted RR of death among 23,275 recipients of a first cadaveric transplant

Progressive renal impairment despite best efforts
Endstage renal dysfunction due to diabetic nephropathy
Required hemodialysis from early 2013

Listed for renal transplantation in early 2013
Pre-Transplant Optimisation

Optimise HIV Treatment

Need for HBV suppression?

Minimise Drug Interactions
### Drug Resistance Interpretation: PR

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PI Major Resistance Mutations:</strong></td>
<td>I84V, L90M</td>
</tr>
<tr>
<td><strong>PI Minor Resistance Mutations:</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Other Mutations:</strong></td>
<td>None</td>
</tr>
</tbody>
</table>

#### Protease Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Resistance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>atazanavir/r (ATV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>darunavir/r (DRV/r)</td>
<td>Low-level resistance</td>
</tr>
<tr>
<td>fosamprenavir/r (FPV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>indinavir/r (IDV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>lopinavir/r (LPV/r)</td>
<td>Intermediate resistance</td>
</tr>
<tr>
<td>nelfinavir (NFV)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>saquinavir/r (SQV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>tipranavir/r (TPV/r)</td>
<td>Intermediate resistance</td>
</tr>
</tbody>
</table>

### Drug Resistance Interpretation: RT

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI Resistance Mutations:</strong></td>
<td>M184V (likely M41L, T215Y)</td>
</tr>
<tr>
<td><strong>NNRTI Resistance Mutations:</strong></td>
<td>K103N</td>
</tr>
<tr>
<td><strong>Other Mutations:</strong></td>
<td>None</td>
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</tbody>
</table>

#### Nucleoside RTI

<table>
<thead>
<tr>
<th>Name</th>
<th>Resistance Level</th>
<th>Non-Nucleoside RTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>lamivudine (3TC)</td>
<td>High-level resistance</td>
<td>efavirenz (EFV) High-level resistance</td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td>Intermediate resistance</td>
<td>etravirine (ETR) Susceptible</td>
</tr>
<tr>
<td>zidovudine (AZT)</td>
<td>High-level resistance</td>
<td>nevirapine (NVP) High-level resistance</td>
</tr>
<tr>
<td>stavudine (D4T)</td>
<td>High-level resistance</td>
<td>rilpivirine (RPV) Susceptible</td>
</tr>
<tr>
<td>didanosine (DDI)</td>
<td>Intermediate resistance</td>
<td></td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td>High-level resistance</td>
<td></td>
</tr>
<tr>
<td>tenofovir (TDF)</td>
<td>Low-level resistance</td>
<td></td>
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</tbody>
</table>
Pre-Transplant Optimisation

Optimise HIV Treatment
- On DRVr monotherapy >2y
- Currently suppressed
- treatment experienced, multiple RAMs

Need for HBV suppression?
- HBVcAB+, sAb+, eAG-, HBV DNA negative

Minimise Drug Interactions
- Immunosuppressants – prednisolone, ciclosporine, sirolimus, MMF
- Other drugs
- will he need INH? IGRA negative
Drug history

HIV:
• DRV/r 800/100mg OD

Renal:
• Aranesp 40mcg OW
• Alfacalcidol 0.25mcg TW
• Ketovite 1 OD
• Calcichew 1 tab TDS
• Furosemide 250mg OM

Hypertension:
• Doxazosin 2mg ON
• Amlodipine 5mg OD

Other:
• Lansoprazole 15mg OD
• Atorvastatin 20mg OD
• Allopurinol 100mg OD
• Folic acid 5mg OD
• Sodium docusate 200mg BD
• Senna 15mg BD
• Lactulose 15ml BD prn

Haemodialysis 3 x weekly
Drug history

HIV:
• DRV/r 800/100mg OD

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• Senna 15mg BD
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Haemodialysis 3 x weekly
Trends in immunosuppressant use
*Maintenance (discharge – 1 year post transplant)*

2005 OPTN/SRTR Annual Report

**1994 – 2003**

**1998 – 2007**
Meier-Kriesche *et al.*
Anticipated Additional medications peri /post transplant:
- Tacrolimus
- Mycophenolate
- Basiliximab
- Entecavir
- Co-trimoxazole
- Isoniazid

<table>
<thead>
<tr>
<th>Immunosuppressants</th>
<th>Darunavir</th>
<th>Ritonavir</th>
<th>Raltegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclosporin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tacrolimus</td>
<td></td>
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</tbody>
</table>
How would you prospectively manage his HIV, HBV and DDIs?

Continue PI/r monotherapy as at present?

Continue PI/r monotherapy + HBV cover?

Change to PI sparing regimen without HBV cover?
  - drugs to partner raltegravir?

Change to PI sparing regimen with HBV cover?
  - with what? TDF / 3TC/FTC / Other?
Increase tacrolimus exposure with ritonavir

- Population PK model developed from historical data, and HIV patients undergoing renal transplantation (N=6)
- 41-fold increase in tacrolimus exposure, $T_\frac{1}{2}$ from 13h to 113h
What dose of tacrolimus would you use with DRV/r?

1. Standard dose (0.2-0.3mg/kg/day)
2. 50% of standard dose
3. 25% of standard dose
4. 5% of standard dose
5. I would undertake pretransplant dose-optimisation
Pretransplant optimisation of tacrolimus dose with bPIs

Multiple doses (4 weeks may not be enough)

Single dose

- MW/Pharm – 2 step Bayesian approach
- 2 compartment model, 1st order absorption
- Predict loading & maintenance to achieve 12.5 – 17.5 ng/mL
- HIV-negative 0.1mg/kg bd (typically 7-8mg bd)
- HIV-positive (N=6) 1.5 - 2mg loading dose, 0.5mg q48h
Optimisation of therapy for transplant

- **Recommended in BHIVA 2005 transplant guidelines**
  
  - Patients selected for transplant should have a trial of four weeks of CNI and MMF immune suppression with therapeutic drug monitoring pre-listing to determine the optimal dose of immune suppressants and PIs/NNRTIs on stable HAART.
  - Once optimum doses have been decided, HAART therapy must not be changed without consultation with the transplant and HIV teams.


- **Not undertaken in this patient**

- **Remained on PI/r + plan to add entecavir post transplant**
Situation

December 2013 - Potential live donor identified

• ABO-incompatible (B-positive to A-positive)

• ART:
  – DRV/r 800/100mg OD
  – VL <40c/ml
  – 184V, 103N, 90M, 84V, X4 + TAMs? + more NNRTI mutations?

• HB SAg +, DNA undetectable

• potential DDIs with immunosuppression
Peri-operative complications

Delayed Graft Functioning

Acute Rejection

Graft Survival

Patient Survival
Surgical complications in 275 HIV-infected liver and/or kidney transplantation recipients

Jack Harbell, MD, a John Fung, MD, PhD, b Nicholas Nissen, MD, c Kim Oltzoff, MD, d Sander S. Florman, MD, e Douglas W. Hanto, MD, PhD, f Jimmy Light, MD, g Steve T. Bartlett, MD, h Andreas G. Tzakis, MD, i Thomas C. Pearson, MD, j Buree Barin, MD, k Michelle E. Roland, MD, l and Peter G. Stock, MD, PhD, a for the HIV TR Investigators, 1 San Francisco and Los Angeles, CA, Cleveland,

**Conclusion.** The rates and outcomes of surgical complications are similar to what has been observed in the non-HIV setting in carefully selected HIV-infected liver and kidney TX recipients. (Surgery 2012;152:376-81.)
High incidence of delayed graft function in HIV-infected kidney transplant recipients

Auxiliadora Mazuecos,1 Ana Fernandez,2 Sofia Zarraga,3 Amado Andres,4 Alberto Rodriguez-Benot,5 Carlos Jimenez,6 Ernesto Gomez,7 Javier Paul,8 Luisa Jimeno,9 Constantino Fernandez,10 Dolores Burgos,11 Ana Sanchez-Fructuoso12 and Lluis Guirado13

- HIV+ (N=36) vs HIV –ve (N=72) 2001-2011
- DGF 52% vs 21%; P<0.0001
Peri-operative complications

Delayed Graft Functioning

- Acute Rejection
- Graft Survival
- Patient Survival
Unadjusted Graft Survival USA 2000 – 2005

Expanded Criteria Donor
Age >60, or Age >50 + medical complexities

Renal transplant outcomes in HIV+ patients

1 and 3 year Graft and Patient survival generally comparable with HIV-negative patients in transplant registries (typically 1y 85-95%, 5y 70-80%, 15y 50-60%)

Acute rejection (within first 12 months) much higher than HIV-negative transplant recipients (US, UK, Spain)

<table>
<thead>
<tr>
<th>Country</th>
<th>Period</th>
<th>HIV+ KT</th>
<th>Acute Rejection</th>
<th>1 year Graft</th>
<th>Patient</th>
<th>3 years Graft</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>2003-2009</td>
<td>150</td>
<td>31%</td>
<td>90.4%</td>
<td>94.6%</td>
<td>73.7%</td>
<td>88.2%</td>
</tr>
<tr>
<td>France</td>
<td>2005-2009</td>
<td>27</td>
<td>15%</td>
<td>98%</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>2001-2009</td>
<td>20</td>
<td>40%</td>
<td>85%</td>
<td></td>
<td>74.4%</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>-2010</td>
<td>35</td>
<td>48%</td>
<td>91.3%</td>
<td>91.3%</td>
<td>84.7%</td>
<td>91.3%</td>
</tr>
</tbody>
</table>

Stock et al NEJM 2010
Gathogo et al Int J STD AIDS 2014
Touzot Am J Transpl 2010
Mazuecos Nephrol Dialysis Transpl 2011
UK Experience (- Dec 2010) : N = 35 (44% live donor)
Favourable graft and patient survival rates and 1 & 3 years
Acute rejection rates (48%) nearly doubled; half within first 3 months

Management difficulties in patients on bPIs:
Tacrolimus – 99% dose reduction (16mg/day vs 0.8mg/week)
In first 8 weeks 48% of time below, and 36% time above therapeutic range

Post transplant

- **12 hours post: Looks amazing!**

- **Renal function rapidly improving**
  - eGFR
    - pre-transplant: <15
    - day 1: 17
    - day 3: 42
    - day 7: 49
    - day 10: 47

- **Discharged Day 8 doing well**
  - Tacrolimus
  - Mycophenolate (MMF)
  - Basiliximab
Week 2

Christmas day - fever, abdominal pain
eGFR 38
CRP ↑↑ 110 (<10)

ultrasound – organising collection around graft, likely haematoma (6 x 7 x 4 cm). US guided drainage commenced on piperacillin-tazobactam

Initial improvement - fever settled CRP still ↑ 136
Anaemia (Hb ↓7.2 g/dL),
thrombocytopenia (platelets ↓ 60 x10^6/mL)
Lactate dehydrogenase ↑↑ 1400 IU/L
Blood film: Red cell fragmentation (schistocytes)
Coombs-negative
Low serum haptoglobin
Normal liver function tests

Thrombotic microangiopathy
Progress

Cause of thrombotic microangiopathy?

• **Sepsis** (thorough infection screen negative)
• **Drug-induced**
  - antibiotics – piperacillin-tazobactam: ↓ platelet preceded
  - entecavir – not recognised side effect
  - tacrolimus – well-established, numerous case reports

Burke GW, et al. Transplantation 1999; 68(9): 1336
Management

- TMA potential life threatening
- Stop tacrolimus
- Need to clear circulating tacrolimus ASAP

- Switch to ABC-3TC-RAL-ETR till tacrolimus clears
- Add prednisolone to cover graft
Progress

Tacrolimus concentration >38 ng/mL (8-15ng/mL)

Switched antibiotics to vancomycin, subsequently to ciprofloxacin
DRVr stopped, switched to abacavir + lamivudine + raltegravir + etravirine

Gradually improved, drain removed
Week 3

Mild thrombocytopenia improving
LDH decreasing (990 IU/mL)
Oral prednisolone to cover graft

Close monitoring of tacrolimus levels
Week 4

off antibiotics, bloods normalised
no evidence of ongoing sepsis / microangiopathy

HIV medications switched back to DRVr
single dose tacrolimus 0.5mg, thereafter guided by TDM
Progress

Continues to make excellent improvement
  - eGFR stable 45-50
  - CD4 >500; VL<45 copies

Discharge Medications

Darunavir 800 mg od
Ritonavir 100 mg od
Labetolol 100 mg od
Entecavir 250 mcg od
Aciclovir 200 mg od
Co-Trimoxazole 480 mg od
Tacrolimus 0.5 mg/week
Prednisolone 10 mg od
Mycophenolate mofetil 1 g bd

Sodium Bicarbonate 1 g tds
Gliclazide 80 mg bd
Alfacalcidol 0.25 mcg 3x/week
Paracetamol 1 g qds prn
Omeprazole 40 mg od
Aspirin 75 mg od
Atorvastatin 20 mg od
Aranesp (Sureclick) 40 mcg monthly SC
Conclusions

Complex case, but manageable
- multiple teams, good communication
- key role of the specialist pharmacist

Unclear reasons for thrombotic microangiopathy
- probably drug-or infection-related

Why high tacrolimus levels?
- dosing error
- unidentified drug interaction
- cellular lysis

Desperate need for organ donors
- Waiting list: UK (6,000), USA (120,990)
- transplants: UK (3,000), USA (14,029)
- need to expand potential donors
Acknowledgements

Clinical Case
Neal Marshall
Sanjay Bhagani

Liverpool Team
David Back
Sara Gibbons
Fiona Marra
Catia Marzolini
Kay Seden
Justin Chiong
Andrew Owen
Marco Siccardi

Others
Marta Boffito