TDF Renal Dysfunction

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SA HIV Clinician Society Conference
Cape Town
27 Nov 2012
Introduction

• Is TDF nephrotoxic?
  – In vitro evidence
  – Epidemiologic evidence
  – Case reports
In vitro studies

• in vitro study
  – TDF is a weak inhibitor of mammalian DNA polymerases
    • Has not decreased mtDNA levels
    • Shows low cytotoxicity
Epidemiology

• Phase I/II
  – N = 49
  – Tenofovir: 75mg, 150 mg, 300 mg, or 600 mg
  – No renal abnormalities at 28 days

• Phase II
  – Schooley, et al, AIDS. 2002
  – RCT
  – N = 181
  – Tenofovir: 75mg, 150 mg, or 300 mg
  – No renal abnormalities after 48 weeks
Conclusion from Clinical Trials

• Double-blind, placebo-controlled studies
  – No difference in incidence of renal events between TDF and placebo groups

• No TDF-related toxic side effects were noted in the recommended drug combination regimes of TDF

But……..
Post-marketing surveillance

- Post-marketing safety data 455,392 person-years of TDF exposure
  - Renal SAE in 0.5%
  - Incr serum creatinine in 2.2%

[Nelson et al. AIDS 2007]
TDF nephrotoxicity

- Potential for nephrotoxicity
  - Similar structure to Adefovir and Cidofovir, known nephrotoxins
  - Accumulation in renal proximal tubule
    - Vd of 0.8 L/kg
    - Minimally protein bound (<8%)
    - Mainly excreted in urine, unchanged form
  - The Mitochondrial Cytopathy Hypothesis
TDF renal toxicity

• Acute kidney injury
• Chronic kidney disease
• Proximal tubular injury, including
  – Fanconi syndrome
  – Isolated hypophosphataemia
  – Decreased bone mineral density
TDF Nephrotoxicity

• Herlitz et al, Kidney Int 2010
  – 13 patients with TDF nephrotoxicity
    • AKI in 9
    • Mild renal dysfunction and subnephrotic proteinuria in 4
    • Glycosuria in 7
  – Renal Histology
    • LM: toxic ATN; PT eosinophilic inclusions
    • EM: mitochondrial enlargement, depletion and dysmorphic changes
  – Outcomes: complete recovery 6; partial recovery 5
LM: TDF Nephrotoxicity

Herlitz et al. Kidney Int, 2010; 78: 1171-1177
EM: TDF Nephrotoxicity

Figure 1. Electron micrographs of proximal tubule cells in a kidney biopsy specimen from a patient with Fanconi syndrome secondary to tenofovir toxicity. (A) Mitochondrial size and morphologic characteristics are highly irregular, with (B) disruption of the normal cristae (arrows) and (C) occasional giant mitochondria. (Scale bars = 500 nm.)
Clinical Studies

• Metanalysis: 17 studies
  – Small but significant loss of kidney function of 3.9ml/min  
    [Cooper et al. Clin Infect Dis, 2010]

• Cohort study 10,000 pts: incr in serum creatinine
  – >0.5mg/dl in 2.2%
  – >2mg/dl in 0.6%  
    [Nelson et al. AIDS. 2007]

• Case series 22 pts with TDF-renal tubular toxicity (1.6% of those on Rx): proteinuria, decr PO4, bone pain due to osteomalacia, incr UPCr, incr serum creatinine  
  [Woodward et al. HIV Med. 2009]
TDF Nephrotoxicity

- Scherzer et al. AIDS 2012
  - 4303 of 10,4841 pts on TDF in VA program 1997-2007
  - 34% incr risk of proteinuria; median time 3.9 years
  - 11% incr risk of rapid decline in renal function
  - 33% incr risk of CKD
TDF- the Johannesburg Experience

- Renal function at ART initiation in 890 pts on TDF 2004-2009 at Themba Lethu Clinic, Helen Joseph Hospital, JHB
  - 64.4% normal renal function
  - 30.4% with eGFR 60-89ml/min
  - 5.2% with eGFR 30-59ml/min

- Outcomes at 48 months
  - Nephrotoxicity 2.4% at median of 3.6 months
  - Death 7.8%
  - Lost to follow up 9.7%

- Risk for nephrotoxicity
  - renal dysfunction
  - Age>40yrs; anaemia; low CD4 count; detectable viral load

Brennan et al. AIDS, 2011;25:1063-1069
Tenofovir & estimated GFR

**Subclinical Renal Tubular Toxicity**

- Severe TDF-tubular toxicity relatively rare; Fanconi Syndrome in <0.1%

- 34/154 (22%) on TDF with normal eGFR had abnormal PT function:
  - Glycosuria
  - Phosphaturia
  - Amino aciduria  
    [Labarga et al. AIDS. 2009]
TDF handling by PT cell
Molecular mechanisms and consequences of TDF nephrotoxicity

Fernandez et al. AIDS Research and Treatment, 2011
Mechanism of TDF nephrotoxicity

• Polymorphism in ABCC2 (gene encoding MRP2): partly responsible for efflux of TDF from PT, resulting in TDF accumulation intracellularly [Rodriguez-Novoa et al, Clin Infect Dis. 2009]

• TDF renal toxic may be decreased by co-adm of drugs inhibiting hOAT1 (transporter responsible for TDF entry into tubular cells) [Izzedine et al. Nat Rev Nephrol, 2009]
Mechanism of Nephrotoxicity

- NRTIs impair mt replication by inhibition of DNA polymerase-y [Brinkman et al. AIDS 1998]
- TDF-exposed rats show low mtDNA copy number and impaired expression of mt-encoded proteins (cytochrome c oxidase1; COX 1) [Lebrecht et al. J Acquir Immune Defic Syndr 2009]
- Murine HIV transgenic model: decr mtDNA in PT and mt ultrastructural abn [Kohler et al. Lab Invest. 2009]
Mitochondrial injury by TDF

- Impairs
  - molecular transport
  - Vitamin D activation
  - Urinary acidification
Patients at risk

- older age
- low body wt
- incr serum creatinine before TDF
- lower CD4
- Co-morbid disease (DM/HPT/HCV infection)
- concurrent use of nephrotoxic drugs or PIs (lopinavir; ritonavir)
- ABCC2 gene polymorphisms
Algorithm for monitoring for TDF renal toxicity

Measure eGFR pre-treatment
- Reduce dose if eGFR < 60ml/min

Assess risk factors for kidney toxicity:
- Age
- Body weight
- eGFR < 90ml/min
- Other renally excreted drugs

Measure every 3 months for 1 year, then biannually:
1. eGFR
2. fractional excretion of phosphate
3. urine protein/creatinine ratio
4. urine glucose
5. tubular proteinuria (e.g. RBP) if available

- Stop drug if significant and sustained changes in 1-4
- Continue with monitoring if small increase in 5 only
- If in doubt, liaise with a nephrologist

Proposal to decrease TDF nephrotoxicity

- Screening of patients for TDF toxicity
- Adjust TDF dose to GFR
- Consider adding EFV to TDF regimens
  - TDF/LAM/EFV < TDF/LAM/NEV renal toxicity
    - Higher GFR
    - lower rates of proteinuria [Manosuthi et al, AIDS Res Ther, 2010]
### Dose Adjustments for ART in CKD and ESRD

<table>
<thead>
<tr>
<th>Name</th>
<th>CKD (adjusted according to creatinine clearance or by eGFR)</th>
<th>Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside or nucleotide analogues</strong></td>
<td></td>
<td></td>
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<tr>
<td>Abacavir</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Azidothymidine (AZT), zidovudine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CrCl ≥ 15 ml/min: no adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 15 ml/min: 100 mg PO q6-8h</td>
<td>HD: dosing independent of dialysis sessions</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>Weight &gt;60 kg: 200 mg PO qd, 150 mg PO qd</td>
<td>HD:100 mg PO q6-8h&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Weight ≤60 kg: 150 mg PO qd</td>
<td>or 300 mg PO qd</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 10 ml/min: 75 mg PO qd</td>
<td>PD: no data</td>
</tr>
<tr>
<td>Emtricitabine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>CrCl &gt; 50 ml/min: no adjustment</td>
<td>CrCl &gt; 50 ml/min: no adjustment</td>
</tr>
<tr>
<td></td>
<td>CrCl 30-49 ml/min: 200 mg PO q48h</td>
<td>HD: 200 mg PO q72h&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CrCl 15-29 ml/min: 200 mg PO q72h</td>
<td>PD: no data</td>
</tr>
<tr>
<td>Lamivudine&lt;sup&gt;a&lt;/sup&gt; (3TC)</td>
<td>CrCl &gt; 50 ml/min: no adjustment</td>
<td>CrCl &gt; 50 ml/min: no adjustment</td>
</tr>
<tr>
<td></td>
<td>CrCl 30-49 ml/min: 150 mg PO qd</td>
<td>HD: 50 mg first dose, then 25 mg PO qd&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CrCl 15-29 ml/min: 150 mg PO qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl 5-14 ml/min: then 30 mg PO qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 5 ml/min: then 30 mg PO qd</td>
<td></td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>CrCl &gt; 50 ml/min: no adjustment</td>
<td>20 mg PO qd&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CrCl 25-50 ml/min: 15-20 mg PO bid</td>
<td>PD: has been used safely</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 25 ml/min: 15-20 mg PO qd</td>
<td></td>
</tr>
<tr>
<td>Tenofovir&lt;sup&gt;d&lt;/sup&gt;</td>
<td>CrCl &gt; 50 ml/min: no adjustment</td>
<td>300 mg PO every 7 days&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CrCl 30-49 ml/min: 300 mg q48h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl 10-29 ml/min: 300 mg q72h</td>
<td></td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>CrCl &gt; 50 ml/min: no adjustment</td>
<td>HD: dose for CrCl &lt; 10 ml/min&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CrCl 10-40 ml/min: 0.75 mg q48h</td>
<td>PD: no data</td>
</tr>
<tr>
<td></td>
<td>CrCl 10-10 ml/min: 0.75 mg q48h</td>
<td></td>
</tr>
<tr>
<td><strong>Non-nucleoside reverse transcriptase inhibitors</strong></td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td><strong>Entry or fusion inhibitor</strong></td>
<td>CrCl ≥ 35 ml/min: no adjustment</td>
<td>Unknown, use with caution</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>CrCl &lt; 35 ml/min: unknown, use with caution</td>
<td></td>
</tr>
<tr>
<td><strong>CCR5 antagonist</strong></td>
<td>No dosage recommendations</td>
<td>No data</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Patients with CrCl &lt; 50 ml/min should receive maraviroc and CYP3A inhibitor only if potential benefit outweighs the risk</td>
<td></td>
</tr>
<tr>
<td><strong>Integrase inhibitor</strong></td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>No adjustment</td>
<td></td>
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</tbody>
</table>

<sup>a</sup> Combination AZT/lamivudine tablets (300mg/150mg) should be administered separately when eGFR<50ml/min
<sup>b</sup> Dose adjustment necessary for any drug from this class in patients with renal dysfunction, hemodialysis or peritoneal dialysis
<sup>c</sup> No dose adjustment necessary for any drug from this class in patients with renal dysfunction, hemodialysis or peritoneal dialysis
<sup>d</sup> Combination emtricitabine/tenofovir tablets (200 mg/300 mg): if CrCl 30–49 ml/min: 1 tablet po q48h; if CrCl < 30 ml/min the combination tablet should not be prescribed

Fig. 56-4. Dose adjustments for ART in CKD and ESRD. FDA recommendations are based on CrCl or eGFR calculated as ml/min, but are likely valid for these expressed as ml/min per 1.73 m². Atripla (efavirenz, tenofovir, and emtricitabine is not recommended for CrCl < 5 ml/min. CrCl, creatinine clearance; HD, hemodialysis; PD, peritoneal dialysis.

Kopp, Fabian and Naicker. Clinical Comprehensive Nephrology, 2010

Deriving estimated glomerular filtration rate (eGFR) using Serum creatinine measurements

- Cockcroft-Gault (CG):
  
  \[
  \text{eGFR} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine} \times 72} \times 0.85 \text{ (for women)}
  \]

- Abbreviated MDRD study equation
  
  \[
  \text{eGFR} = 186 \times \text{S-creatinine}^{1.154} \times \text{age}^{0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)}
  \]
Fanconi Syndrome

Hypophosphatemia, acidosis, glycosuria, aminoaciduria, hypokalemia = FANCONI SYNDROME
Tenofovir related renal toxicity

Dysfunction of proximal renal tubules - unclear mechanism

“wasting” of substances normally reabsorbed in PT
- small proteins
- glucose
- phosphates
- bicarbonates

secondary glomerular dysfunction

Reduced Creatinine Clearance (CKD)
Disordered Bone Metabolism

Proteinuria
Glycosuria
Phosphaturia
Metabolic acidosis
What is tenofovir disoproxil fumarate (TDF)?

- Orally administered pro-drug of tenofovir
- Tenofovir is a nucleotide analogue inhibitor of reverse transcriptase (NtRTI)
  - Others in the family are Adefovir and Cidofovir, well described nephrotoxins
  - Tenofovir similar to Adefovir
  - The only NtRTI used for treatment of HIV
TDF is eliminated through the Kidney

Potential for accumulation of high concentration of TDF in proximal tubule cells
TDF

• **Single Agent**
  – Viread
    • marketed for the treatment of HIV since 2001

• **Combination**
  – Truvada
    • Fixed-dose combination
      – TDF and emtricitabine (NRTI), 2004
  – Atripla
    • Fixed-dose triple combination of
      – TDF, emtricitabine (NRTI) and efavirenz (NNRTI), 2006
Conclusion from case reports

• Potential role of drug interactions
  – Ritonavir
    • has been shown to increase serum TDF by >30%
    • Inhibitor of MRP-2 -> increase proximal tubular concentration of TDF by decreasing secretion
  – Didanosine
    • Coadministration with TDF may increase serum concentration of didanosine -> proximal tubular dysfunction

• Polymorphism in the renal tubular drug transporter
  – variant MRP 2 or 4
EM: TDF Nephrotoxicity

Herlitz et al. Kidney Int, 2010
TDF transport in renal PT

Hall et al. Am J Kid Dis. 2011