RENAL DISEASE AND HIV

Sanjay Pujari MD
Institute of Infectious Diseases, Pune India
HIVAN
HIVICK
Co-morbid DM, HTN

Outline

- Glomerulus
- Bowman capsule
- Tubules
- Tubular Interstitial Nephritis
HIVAN and HIVICK

**HIVAN**

- Collapsing FSGS, microcysts in tubules, interstitial inflammation *(Kidney Int. 1999;56(6):2203)*
- Incidence declined after cART *(AIDS. 2004;18(3):541)*
- Advanced HIV disease, Heavy proteinuria, rapid course *(Nephrol Dial Transplant. 2012 Mar;27(3):1114-21)*
- Treatment: cART, ACE/ARBs and steroids *(Adv Chronic Kidney Dis. 2010 Jan;17(1):52-8)*

**HIVICK**

Progression to ESRD: HIVAN vs HIVICK

Impact of cART on ESRD d/t HIVAN

Impact of cART on ESRD d/t HIVICK

HIV/HCV and the kidney

![Graph showing the probability of developing end-stage kidney disease over time for individuals with HIV+HCV+ and HIV+HCV-](image-url)
Outline

- HIVAN
- HIVICK
- Co-morbid DM, HTN

- Tubular Interstitial Nephritis

- Nephrotoxic Drugs
- ARVs
- Others
Incidence rate of CKD per yr of exposure to ARVs
ARV exposure and rates of progression to eGFR<70 ml/min
Higher risk of renal impairment with TDF in LMICs?

![Graph showing comparison of renal impairment progression in Royal Free and Pune.](image)

- **Pune**: 448, 414, 365, 295, 174, 103
- **RFH**: 424, 399, 339, 270, 172, 103

*Source: BMC Infectious Diseases 2014 14:173*
Decline in eGFR over 8 years in Japan

AIDS Patient Care STDS. 2017 Mar;31(3):105-112
## Risk factors for CKD on ART: Japan

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF use, relative to the control</td>
<td>1.8</td>
<td>1.00–3.13</td>
<td>0.052</td>
</tr>
<tr>
<td>Age per 1-year increase</td>
<td>1.1</td>
<td>1.04–1.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.6</td>
<td>0.18–1.67</td>
<td>0.30</td>
</tr>
<tr>
<td>Baseline eGFR per 1-mL/min/1.73 m² increase</td>
<td>0.9</td>
<td>0.89–0.93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight per 1-kg increase</td>
<td>1.0</td>
<td>0.98–1.03</td>
<td>0.66</td>
</tr>
<tr>
<td>Use of nephrotoxic drugs</td>
<td>0.5</td>
<td>0.24–0.89</td>
<td>0.020</td>
</tr>
<tr>
<td>Use of ritonavir-boosted protease inhibitors</td>
<td>0.7</td>
<td>0.34–1.31</td>
<td>0.24</td>
</tr>
<tr>
<td>CD4 count per 1-µL increase</td>
<td>1.0</td>
<td>1.00–1.00</td>
<td>0.013</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.2</td>
<td>1.10–4.38</td>
<td>0.026</td>
</tr>
<tr>
<td>cART duration (per day)</td>
<td>1.0</td>
<td>1.00–1.00</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Risk factors for CKD: Vietnam

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th></th>
<th></th>
<th>Multivariate analysis</th>
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<th>p value</th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>Age per year-increase</td>
<td>1.135</td>
<td>1.102 - 1.168</td>
<td>1.229</td>
<td>1.170 - 1.291</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3.150</td>
<td>1.786 - 5.556</td>
<td>2.124</td>
<td>0.892 - 5.056</td>
<td>0.089</td>
<td></td>
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<tr>
<td>Body weight per 1 kg-decrement</td>
<td>1.170</td>
<td>1.119 - 1.223</td>
<td>1.286</td>
<td>1.193 - 1.386</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Use of TDF</td>
<td>2.670</td>
<td>1.522 - 4.685</td>
<td>2.715</td>
<td>1.028 - 7.168</td>
<td>0.044</td>
<td></td>
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<tr>
<td>Use of Lopinavir</td>
<td>2.257</td>
<td>1.165 - 4.370</td>
<td>1.439</td>
<td>0.460 - 4.497</td>
<td>0.531</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>3.180</td>
<td>1.251 - 8.084</td>
<td>1.614</td>
<td>0.353 - 7.383</td>
<td>0.537</td>
<td></td>
</tr>
<tr>
<td>AIDS defining disease</td>
<td>2.417</td>
<td>1.160 - 5.035</td>
<td>2.042</td>
<td>0.628 - 6.643</td>
<td>0.236</td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count per cell/μl</td>
<td>1.000</td>
<td>0.998 - 1.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA level per log 10 copies/ml</td>
<td>1.055</td>
<td>0.641 - 1.736</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of ART per year</td>
<td>1.138</td>
<td>0.982 - 1.318</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of ccrtrimoxazole</td>
<td>1.740</td>
<td>0.966 - 3.134</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PLoS One. 2013;8:e79885*
A5202s: TDF vs ABC
TDF nephrotoxicity: Clinical aspects

- **Proximal tubulopathy**
  - Preserved GFR
    - Fanconi’s syndrome
      - Partial/complete
  - Decline in GFR
    - AKI
    - CKD
    - Decline in eGFR
    - Fanconi’s syndrome
Phosphaturia and BMD

Spearman’s rho = -0.33; $P < 0.01$

AIDS 2016 Jun 1;30(9):1423-31
eGFR and CV events
eGFR/aUR and CV events/heart failure

Circulation. 2010 Feb 9;121(5):651-8
Monitoring S.Creat in TAHOD

<table>
<thead>
<tr>
<th>Year on TDF</th>
<th>Person-years of observation</th>
<th>Number of S-Cr assessments</th>
<th>Crude rate (per person-year)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>3,041.02</td>
<td>6,260</td>
<td>2.06</td>
<td>(2.01, 2.11)</td>
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<tr>
<td>2nd</td>
<td>1,270.4</td>
<td>2,236</td>
<td>1.76</td>
<td>(1.69, 1.83)</td>
</tr>
<tr>
<td>3rd</td>
<td>824.6</td>
<td>1,445</td>
<td>1.75</td>
<td>(1.66, 1.85)</td>
</tr>
<tr>
<td>4th</td>
<td>515.41</td>
<td>781</td>
<td>1.52</td>
<td>(1.41, 1.63)</td>
</tr>
<tr>
<td>5th</td>
<td>220.93</td>
<td>361</td>
<td>1.63</td>
<td>(1.47, 1.81)</td>
</tr>
<tr>
<td>6th-10th</td>
<td>121.81</td>
<td>228</td>
<td>1.87</td>
<td>(1.64, 2.13)</td>
</tr>
</tbody>
</table>

TDF, tenofovir disoproxil fumarate; S-Cr, serum creatinine; CI, confidential interval.

doi:10.1371/journal.pone.0161562.t003
TDF nephrotoxicity: Monitoring eGFR

AIDS. 2012;26:1781–1788.
Cyst-C associated with T cell activation

TDF nephrotoxicity: Monitoring proteinuria

TDF nephrotoxicity: Monitoring proteinuria

Urinary B2microglobulin after TDF predicts decline in eGFR

eGFR recovery after TDF discontinuation

ATV and urolithiasis
DTG & COB: clinically irrelevant Creat elevation

Creatinine Transport Pathway

- Creatinine
- OAT2
- OCT3
- OCT2
- MATE2
- MATE1
- Cobicistat
- Cimetidine
- Trimethoprim
- Ritonavir
- Rilpivirine
- Dolutegravir

Blood (Basolateral) → Urine (Apical)

Active Tubular Secretion

Infect Dis Ther (2013) 2:111–122
SAILING: DTG vs RAL (experienced, INSTI-naive)
AV grafts in PLHIV: Outcomes

AV fistulas in PLHIV: Outcomes

Higher peritonitis risk on CAPD
Kidney transplantation: Patient survival

Kidney transplantation: Graft survival

Kidney transplantation: key issues

- Higher acute rejection rates *(Transplantation 2014; 97:446–50)*
  - Induction: Did not receive lymphocyte depletion agents
  - Maintenance: sirolimus based


  - TMP-SMX, Valgan, Fluconazole, INH

- Delayed graft function as risk for allograft failure *(Transpl Int 2013; 26:893–902)*

- DDIs
  - Calcinuerin inhibitors: PI/r *(AIDS Patient Care STDs 2012; 26:568–81)*
  - CCR5 blockade as an asset *(Lancet 2001; 357:1758–61)*
Kidney transplantation: HIV+ donors

A Graft Survival

B Patient Survival

Minimizing renal toxicity with ART: Strategies

• TAF

• nRTI sparing regimens
  • LPV/r + 3TC
  • DRVr + RAL
  • DTG + 3TC
  • RPV + DTG

• PK monitoring of TDF \((AIDS. 2016;30(4):609-18)\)

• Minimize CKD and CVD risk factors
TAF vs TDF: Renal toxicity

TAF vs TDF: ARV naïve

B. Proteinuria and Albuminuria

Proteinuria (UPCR)

Median % Change from Baseline (Q1, Q3)

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n 866</td>
<td></td>
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<td></td>
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<tr>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n 866</td>
<td></td>
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</tr>
</tbody>
</table>

Table: Baseline (mg/g)

- 44
- 5

Albuminuria (UACR)

Median % Change from Baseline (Q1, Q3)

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n 851</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n 850</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table: Baseline (mg/g)

- 5
- 5

TAF vs TDF: ARV naïve

C Tubular Proteinuria

- RBP/Cr
  - Baseline (µg/g): 64, 67
  - Median % Change from Baseline (Q1, Q3)
    - BL: 0
    - Week 48: 20
    - Week 96: 40
  - p < 0.001

- β-2M/Cr
  - Baseline (µg/g): 101, 103
  - Median % Change from Baseline (Q1, Q3)
    - BL: 0
    - Week 48: -30
    - Week 96: -40
  - p < 0.001
Switching from TDF to TAF

- eGFR Median Change (mL/min):
  - F/TAF: 10.0
  - F/TDF: 4.0

- Urine protein to creatinine ratio (% median change):
  - P/Cr: *2.7
  - Alb/Cr: *3.4
  - RBP/Cr: *42.6
  - β2MG/Cr: *46.8

* p < 0.001
Cr: creatinuria
Switch to TAF in renal impairment

![Graph showing median change from baseline in eGFR in mL/min/1.73 m² (Q1, Q3) over weeks 0 to 96.]

- Pre-switch TDF
  - Baseline: 75.4 (60.9, 86.2)
  - Week 96: 80.1 (65.8, 95.7)
- Without Pre-switch TDF
  - Baseline: 60.4 (47.7, 75.0)
  - Week 96: 62.3 (50.4, 77.9)

J Acquir Immune Defic Syndr. 2017 Feb 1;74(2):180-184
Switch to TAF in renal impairment
TAF: Unanswered questions

- Real world practice over long term (late failures)
  - Long term renal side effects of TDF were not seen in pivotal studies but in cohorts like DAD and EUROSIDA

- TAF in CKD not studied in RCTs

- TAF use in special situations e.g. concomitant nephrotoxic medications

- Most studies report on markers of renal and bone dysfunction rather than hard clinical measures

- Can TAF be substituted amongst patients with TDF nephrotoxicity?

- TAF DDIs esp RMP
Summary: Implications for practice (1)

- HIVICK more common than HIVAN in untreated HIV infection in Asia

- CKD has implications
  - Bone health
  - CV outcomes

- Aging and other comorbidities e.g. DM contribute to renal disease in cART era

- ARVs associated with significant nephrotoxicity
  - TDF, ATV/r
Summary: Implications for practice (2)

- Incidence of TDF renal toxicity seems higher in Asia

- Monitoring for renal disease challenging
  - eGFR equations underestimate true GFR
  - Dipstick underestimates proteinuria

- Dialysis outcomes are marginally poor while transplantation outcomes good

- Prevention strategies include access to safer ARVs e.g. TAF and novel strategies e.g. n(t)RTI sparing regimens
Factors associated with development of CKD

**HIV Infection**
- HIV replication
- Apoptosis (Vpr/Nef)
- De-differentiation (Nef/Tat)
- Immunocomplex formation

**General risk factors**
- Age
- Diabetes/Hypertension
- Ethnicity
- HCV infection

**Immune activation**
- Immunocomplex formation

**cART**

**Kidney disease**