The Double-Edged Sword: Nephrotoxicity of Anti-retroviral Therapy

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Johns Hopkins
Disclosure of Interests

• Gilead: subcontract Research Grant to the Institution
Objectives

Review classes of Antiretroviral treatment (ART)

Evaluate patterns of renal injury with ART

Outlines current renal guidelines on ART use/management

KDIGO Controversies Conference on HIV-Related Kidney Diseases
March 17-20, 2017 | Yaoundé, Cameroon
Deferred treatment

Early treatment

cART toxicities
Metabolic derangements

HIVAN
## Initial Regimens: First-Line

**DHHS Guidelines, July 2016**

<table>
<thead>
<tr>
<th>INSTI based</th>
<th>PI based</th>
</tr>
</thead>
<tbody>
<tr>
<td>- DTG/ABC/3TC; only if HLA-B*5701 negative (AI)</td>
<td>- DRV/r (QD) + TDF/FTC (AI) or TAF/FTC (AII)</td>
</tr>
<tr>
<td>- DTG (QD) + TDF/FTC (AI) or TAF/FTC (AII)</td>
<td></td>
</tr>
<tr>
<td>- EVG/CObI/TAF/FTC</td>
<td></td>
</tr>
<tr>
<td>- EVG/CObI/TDF/FTC; only if pre-ART CrCl &gt;70 mL/min (AI)</td>
<td></td>
</tr>
<tr>
<td>- RAL + TDF/FTC (AI) or TAF/FTC (AII)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:**

3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency
July 2016 Updates on Recommended Regimens for First-line ART


<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>DTG/ABC/3TC</td>
<td></td>
<td></td>
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<tr>
<td>DTG + TAF/FTC</td>
<td></td>
<td></td>
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<tr>
<td>DTG + TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVG/COBI/TAF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVG/COBI/TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL + TAF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL + TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV + RTV + TAF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV + RTV + TDF/FTC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DHHS[1]**
- Recommended regimens include 3 INSTIs and 1 boosted PI
- Primary change since Jan 2016 update is addition of TAF/FTC

**IAS-USA[2]**
- All recommended regimens include INSTI + TAF/FTC or ABC/3TC
- Major changes since 2014 update include removal of NNRTIs, boosted PIs, and TDF

Preferred/recommended ▶ Alternative
ART AND AKI
Causes of Acute Renal Failure


---

Direct Tubular Cell Toxicity and Necrosis
Acute Tubular Necrosis

Intratubular Crystal Deposition
Crystal Nephropathy

Allergic Reaction in the Interstitium
Allergic Interstitial Nephritis

Obstruction from Stones
Postrenal Azotemia

↓ RBF from

KDIGO Controversies Conference on HIV-Related Kidney Diseases
March 17-20, 2017 | Yaoundé, Cameroon
ART associated with AKI

Protease inhibitors
- Crystal-induced nephropathy, AIN

Tenofovir
- AKI; Fanconi syndrome; nephrogenic DI

Integrase inhibitors
- Rhabdomyolysis/pigment nephropathy

NNRTIs
- Nephrolithiasis

NRTIs
- Nephrolithiasis; AIN; rhabdomyolysis
Crystalluria and Stone Formation

Indinavir

240 Patients:
• 20%: crystalluria
• 3%: uroliths

**Risk factors:**
• Alkaline urine pH>6,
• low body mass,
• dose of 1000 mg or more twice daily,
• warm weather

*Annals of Internal Medicine, 15 July 1997. 127:119-125*

*NEJM, Hanabusa et al., February 1999*
Urolithiasis in HIV positive patients treated with atazanavir

**Prevalence:**
- 0.97% (11/1134) patients who were treated with ATV from March 2004 through February 2007

**Risk factors:**
- Alkaline pH: ≥6
- Duration on treatment

*Couzigou et al. CID 2007:45 (15 October)*
Tenofovir renal toxicity

- Reported in up to 15% of patients treated for 2-9 years.
  - Acute renal failure
  - Fanconi syndrome
  - Nephrogenic diabetes insipidus
  - Chronic kidney disease

Atta M. et al. Seminars in Nephrology 2008;6
Izzedine et.al. AJKD 2005;45
Winston, et.al. HIV Med 20067
Rosiglitazone reverses tenofovir-induced nephrotoxicity

Model for TDF transport in the proximal tubule

Adapted from Mitema and Atta *Current Drug Metabolism, 2015*

Proximal Tubule

- **OAT1**
- **OAT3**
- **OCT2**
- **MATE1**
- **MRP4**
- **MRP2**

**Tenofovir**

**Creatinine**

**Blood (Basolateral)**

**Urine (Apical)**

**Active Tubular Secretion**

Adapted from Mitema and Atta *Current Drug Metabolism, 2015*
Herlitz et al KI 2010
Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy


PRTD was defined on the basis of the presence of at least 2/5 criteria (399 patients):

- ↑ in FE phos, with low sr. phos. <0.80 mmol/l
- Non-diabetic glucosuria
- Metabolic acidosis (pH <7.34 and sr. bicarb. <22 mmol/l)
- Ratio B2-microglobulinuria/ur. cr. >40.3 mg/l
- Low sr. uric acid with ↑ FE uric acid >15%
Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy


- **Prevalence: 6.5%**

<table>
<thead>
<tr>
<th>Final model</th>
<th>OR</th>
<th>(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.28</td>
<td>(1.05–1.58)</td>
<td>0.017</td>
</tr>
<tr>
<td>TDF</td>
<td>1.23</td>
<td>(1.02–1.47)</td>
<td>0.028</td>
</tr>
<tr>
<td>ATV</td>
<td>1.28</td>
<td>(1.04–1.58)</td>
<td>0.021</td>
</tr>
</tbody>
</table>
Prevalence of TDF renal tubular dysfunction

**Ezinga et al. Antiviral Therapy 2014**
- 161 patients (mean age 46, 85% men, mean TDF exposure 40 months)
- RTD: urine α1-microglobulin/Cr. >15mg/10mmol, FEPO4>20% with low serum PO4, FEUric acid >10% with low serum, glucosuria
- 62.7% had one criteria, 10.6% had 2 or more criteria

**Hamzah et al. AIDS 2015**
- 293 men (mean age 48, 94% White, median TDF exposure 2.1 years)
- RTD: retinol-binding protein/creatinine ratio (RBPCR) or FEPO4>20% with low serum PO4
- 22.5% had RBPCR-defined RTD, 6.5% >5 fold increase, and 12.3% had FEPO4-defined RTD
Clinical course of Proximal tubular dysfunction


15 patients (73% male) with FEPO2>20% (mean age 56, 80% White ethnicity, mean TDF exposure 64 months).

Mean FEPO4 34%.

Mean eGFR at TDF start 104 mL/min/1.73m2 with a gradual decline to 69 mL/min/1.73m2 by the time of TDF discontinuation.

None returned to baseline eGFR after discontinuation.
Predictors of Kidney Tubular Dysfunction in HIV-Infected Patients Treated with TDF: A Pharmacogenetic Study

Rodríguez-No´voa et al. CID 2009:48 (1 June)

115 HIV-infected patients were examined, of whom 19 (16.5%) had RTD:

**Adjusted analysis:**
- Older age per 1y (OR, 1.1; 95% CI, 1.0–1.2; p=0.024)
- Lower body weight/1kg (OR, 0.9; 95% CI, 0.8–0.9; p=0.048)
- Genotype CC at ABCC2 position 24 (OR, 5; 95% CI, 1.2–21; p=0.027)
Polymorphisms associated with renal adverse effects of antiretroviral therapy in a Southern Brazilian HIV cohort

da Rochaa et al. Pharmacogenetics and Genomics 2015
Risk Factors influencing TDF elimination

- Low body weight
- Underlying kidney disease
- Use of DDI
- Use of nephrotoxic drugs
- Low CD4 count
- HCV coinfection
- DM

Adapted from Expert Opin. Drug Saf. 2010;9:545-559
ART AND CKD
Chronic kidney disease and antiretroviral drug use in HIV-positive patients

Mocroft et al. AIDS 2010, EuroSIDA Study Group

3.3% over a median follow-up of 3.7

N=6843  6598  5323  3789  2298
## Hazard of CKD incidence

Mocroft et al. AIDS 2010, EuroSIDA Study Group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>1.16</td>
<td>1.06-1.25</td>
</tr>
<tr>
<td>Indinavir</td>
<td>1.12</td>
<td>1.06-1.18</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>1.21</td>
<td>1.09-1.34</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>1.08</td>
<td>1.01-1.16</td>
</tr>
</tbody>
</table>
# Tenofovir exposure and risk of outcomes

Scherzer et al. AIDS 2012

- **10,841 HIV-infected VA patients 1997-2007**
- **Median follow-up: 3.9 years (proteinuria), 5.5 years (CKD)**

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>Proteinuria (n=3400 events)</th>
<th>Rapid decline (n=3078 events)</th>
<th>CKD (n=1712 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cumulative exposure to tenofovir (per year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.34 (1.25–1.45)***</td>
<td>1.11 (1.03–1.18)*</td>
<td>1.23 (1.12–1.35)***</td>
<td></td>
</tr>
<tr>
<td><strong>Ever exposure to tenofovir (versus never)</strong></td>
<td></td>
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<tr>
<td>1.68 (1.52–1.85)***</td>
<td>1.36 (1.23–1.50)***</td>
<td>1.38 (1.20–1.57)***</td>
<td></td>
</tr>
</tbody>
</table>
NEW AGENTS

Dolutegravir: Integrase inhibitor
Cobicistat: Pharmacoenhancer
Model of organic anion transporters in proximal tubule

Adapted from Mitema and Atta *Current Drug Metabolism, 2015*

Proximal Tubule

- **OAT1**
- **OAT3**
- **OCT2**
- **MATE1**
- **MRP4**
- **MRP2**

**Blood**

- **Creatinine**
- **Tenofovir**

**Mitochondria**

- **Cobicistat**
- **Ritonavir**
- **Cimetidine**
- **Trimethoprim**

**Urine**

- **Creatinine**

**Active Tubular Secretion**

**Blood** (Basolateral)
Tenofovir Alafenamide (TAF) vs TDF in Treatment-Naive Pts

Parallel, randomized, double-blind, active-controlled phase III studies

Primary endpoint HIV-1 RNA at Week 48

eGFR > 50 ml/m

**Sax P et al. The Lancet, 2015**

*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm.
†Discontinued for AE, death, or missing data.
Changes in quantitative proteinuria at week 48

Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Patients With Renal Impairment: 48-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study

Anton Pozniak, MD,* Jose R. Arribas, MD,† Joseph Gathe, MD,‡ Samir K. Gupta, MD,§ Frank A. Post, MD,∥ Mark Bloch, MD,¶ Anchalee Avihingsanon, MD,# Gordon Crofoot, MD,** Paul Benson, MD,†† Kenneth Lichtenstein, MD,‡‡ Moti Ramgopal, MD,§§ Ploenchait Chetchotisakd, MD,|| Joseph M. Custodio, PhD,¶¶ Michael E. Abram, PhD,||| Xuelian Wei, PhD,|||| Andrew Cheng, MD, PhD,|||| Scott McCallister, MD,|||| Devi SenGupta, MD,|||| and Marshall W. Fordyce, MD,|||| for the GS-US-292-0112 Study Team

N= 242, Cr. Cl. 30-69; <50=80, >50 162

Primary endpoint: Change in GFR from baseline
<table>
<thead>
<tr>
<th>TABLE 2. Estimated GFR: Change From Baseline to Weeks 24 and 48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Change (Q1, Q3) (mL/min)</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Total, N = 242</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>&lt;50 mL/min, n = 80</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>≥50 mL/min, n = 162</strong></td>
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<td></td>
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<tr>
<td><strong>TDF Containing, n = 158</strong></td>
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<td></td>
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<tr>
<td><strong>Non-TDF Containing, n = 84</strong></td>
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<td></td>
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<tr>
<td><strong>Change at week 24</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>eGFR&lt;sub&gt;CG&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>-0.4 (-4.8, 4.5)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>eGFR&lt;sub&gt;CKD-EPI&lt;/sub&gt;&lt;sub&gt;Cr&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>-1.8 (-6.1, 4.9)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>eGFR&lt;sub&gt;CKD-EPI&lt;/sub&gt;&lt;sub&gt;kysC&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>+3.8 (-4.8, 11.2)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Change at week 48</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>eGFR&lt;sub&gt;CG&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>-0.6 (-5.4, 5.4)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>eGFR&lt;sub&gt;CKD-EPI&lt;/sub&gt;&lt;sub&gt;Cr&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>-1.8 (-7.9, 4.1)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>eGFR&lt;sub&gt;CKD-EPI&lt;/sub&gt;&lt;sub&gt;kysC&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>+1.6 (-7.4, 11.9)</td>
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</tr>
</tbody>
</table>

**Figure:**

Bar charts showing median changes in kidney function over weeks 24 and 48 for different groups.
### TDF vs TAF

<table>
<thead>
<tr>
<th>TDF</th>
<th>TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg daily</td>
<td>10-25 mg daily</td>
</tr>
<tr>
<td>No systemic metabolism</td>
<td>Hepatic and mononuclear cell metabolism to TFV</td>
</tr>
<tr>
<td>Rapidly hydrolyzed in plasma</td>
<td>Prolonged stability in plasma</td>
</tr>
<tr>
<td>High circulating TFV</td>
<td>Reduced systemic exposure to TFV</td>
</tr>
</tbody>
</table>
For TAF:

Hepatic impairment decreases AUC of active metabolite (TFV) by 11%.

AUC of active metabolite (TFV) increases by 5.7 fold with renal impairment (CrCl 15mL/min – 90mL/min)
Intracellular accumulation of TFV and TAF in cells expressing OAT transporters

Transient OAT expression

<table>
<thead>
<tr>
<th></th>
<th>TFV</th>
<th>TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>OAT1</td>
<td>83</td>
<td>0.4</td>
</tr>
<tr>
<td>OAT3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Stable OAT expression

<table>
<thead>
<tr>
<th></th>
<th>TFV</th>
<th>TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>OAT1</td>
<td>1</td>
<td>4.4</td>
</tr>
<tr>
<td>OAT3</td>
<td>74</td>
<td>1.3</td>
</tr>
</tbody>
</table>

March 24, 2017
WHAT SHOULD WE DO?
D:A:D: ARV Exposure and Risk Score of CKD

17,954 HIV+ individuals with eGFR > 60 ml/min/1.73 m²

Enrolled in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D)

641 developed CKD during median follow-up of 6.1 years.

Risk for CKD

- Older age, Female, IVDU, lower CD4 count nadir
- Lower baseline eGFR, HCV coinfection, HTN, DM, and CVD.


doi:10.1371/journal.pmed.1001809

http://127.0.0.1:8081/plosmedicine/article?id=info:doi/10.1371/journal.pmed.1001809
## Chronic Kidney Disease Tool

**Gender:**
- Female
- Male

**Age at the time when eGFR was measured:**

**Date of birth (yyyy-mm-dd):**

**Date when eGFR was measured (yyyy-mm-dd):**

**IDU:**
- Yes
- No

**HCV:**
- Yes
- No

**eGFR:**

**Nadir CD4:**

If the answer to any of the questions below is unknown, please do not enter any further data; your risk-score for CKD will be calculated without using these variables.

**Diabetes:**
- Yes
- No

**History of Cardiovascular Disease**
- Yes
- No

**Is the answer yes to at least one of the following 3 questions:**
- Is the diastolic blood pressure >100 mm/Hg (10 mm/Hg or 13.33 kPa)?
- Is the systolic blood pressure >150 mm/Hg (15 mm/Hg or 20.00 kPa)?
- Is the person using antihypertensive medication or ACE inhibitors?

---

**KDIGO Controversies Conference on HIV-Related Kidney Diseases**

March 17-20, 2017 | Yaoundé, Cameroon
## Chronic Kidney Disease Tool

### Gender:
- ○ Female
- ○ Male

### Age at the time when eGFR was measured:
- 50

### Date of birth (yyyy-mm-dd)

### Date when eGFR was measured (yyyy-mm-dd)

### IDU:
- ○ Yes
- ○ No

### HCV:
- ○ Yes
- ○ No

### eGFR:
- 70
  - eGFR Calculator

### Nadir CD4:
- 200

---

If the answer to any of the questions below is unknown, please do not enter any further data; your risk-score for CKD will be calculated without using these variables.

### Diabetes:
- ○ Yes
- ○ No

### History of Cardiovascular Disease
- ○ Yes
- ○ No

### Is the answer yes to at least one of the following 3 questions:
- Is the diastolic blood pressure >100 mm/Hg (10 mm/Hg or 13.33 kPa)?
- Is the systolic blood pressure >150 mm/Hg (15 mm/Hg or 20.00 kPa)?
- Is the person using antihypertensive medication or ACE inhibitors?
### Chronic Kidney Disease Tool

<table>
<thead>
<tr>
<th><strong>Gender:</strong></th>
<th>○ Female ○ Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at the time when eGFR was measured:</strong></td>
<td>50</td>
</tr>
<tr>
<td><strong>Date of birth (yyyy-mm-dd):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Date when eGFR was measured (yyyy-mm-dd):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IDU:</strong></td>
<td>○ Yes ○ No</td>
</tr>
<tr>
<td><strong>HCV:</strong></td>
<td>○ Yes ○ No</td>
</tr>
<tr>
<td><strong>eGFR:</strong></td>
<td>70</td>
</tr>
<tr>
<td><strong>Nadir CD4:</strong></td>
<td>200</td>
</tr>
</tbody>
</table>

**Basic result**

Based on the information you have put into the CKD risk-score calculator, you are estimated to have a 86% chance of developing CKD in the next 5 years.

Some antiretrovirals may be associated with higher risks of CKD, and adding or starting these may increase your risk of CKD, as shown below.

<table>
<thead>
<tr>
<th>ARV started or added to regimen</th>
<th>Chance of CKD over the next 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>100%</td>
</tr>
<tr>
<td>Atazanavir with ritonavir</td>
<td>100%</td>
</tr>
<tr>
<td>Atazanavir without ritonavir</td>
<td>100%</td>
</tr>
<tr>
<td>Lopinavir with ritonavir</td>
<td>100%</td>
</tr>
<tr>
<td>Any other ritonavir boosted protease inhibitor</td>
<td>100%</td>
</tr>
</tbody>
</table>

**When more than one of the potentially nephrotoxic antiretrovirals are added, the risk of CKD may increase even further. Please indicate if you are adding or starting more than one of these antiretrovirals at the same time**

- [ ] Tenofovir
- [ ] Atazanavir with ritonavir
- [ ] Atazanavir without ritonavir
- [ ] Lopinavir with ritonavir
- [ ] Any other ritonavir boosted protease inhibitor

---

**Diabetes:** ○ Yes ○ No

**History of Cardiovascular Disease:** ○ Yes ○ No

**Is the answer yes to at least one of the following 3 questions:**
- Is the diastolic blood pressure >100 mm/Hg (10 mm/Hg or 13.33 kPa)?
- Is the systolic blood pressure >150 mm/Hg (15 mm/Hg or 20.00 kPa)?
- Is the person using anti-hypertensive medication or ACE inhibitors?
Screen for kidney disease: when ART is initiated or changed, and at least twice yearly in stable HIV-infected patients.

In patients with eGFR <60 mL/minute/1.73 m2, we recommend avoiding TDF when feasible.

In TDF-treated patients with confirmed GFR decline by >25% or to <60 mL/minute/1.73 m2, we recommend substituting alternative ART for TDF, particularly in those with evidence of PTD.

The necessity for differential dose adjustments of one or more components usually precludes the use of fixed-dose combinations in patients with moderately to severely impaired kidney function.
ART and Kidney

Renal toxicities are rare with NNRTIs, Entry and Integrase inhibitors.

Among PIs, renal toxicities have mainly been reported with IDV and ATZ.

TDF is the most nephrotoxic used today.

CKD 5-year risk score can be a helpful tool.

TAF can be nephrotoxic in susceptible host.
THANK YOU!