Evaluation and Management of Bone and Renal Toxicities in HIV+ Patients on Antiretroviral Therapy

Steven C. Johnson M.D.
Faculty Development Conference
August 7, 2014
Financial Disclosures

• Served as a consultant, attending advisory board meetings for ViiV Healthcare and Gilead Sciences
Objectives

• Identify potential causes of chronic renal disease and metabolic bone diseases in HIV-infected patients on antiretroviral therapy.

• Learn interventions in the management of bone and renal toxicities including changes in ARV agents or dosing of ART, and other therapies to treat these complications.
21st Conference on Retroviruses and Opportunistic Infections, March 3-6, 2014, Boston, Massachusetts
Which of the following best describes your current role in health care?

A. Physician/NP/PA
B. Nurse
C. Pharmacist
D. Social Worker
E. Case Manager
F. Health Educator
G. Other
Trends in Annual Death Rate Among People Living with HIV by Gender, Colorado, 1988-2011, Deaths per 1000 persons

Source: CDPHE
<table>
<thead>
<tr>
<th>Co-infections</th>
<th>Non-infectious diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>•  Hepatitis B</td>
<td>•  Mental health conditions</td>
</tr>
<tr>
<td>•  Hepatitis C</td>
<td>•  Alcohol and tobacco use</td>
</tr>
<tr>
<td>•  HPV-related diseases</td>
<td>•  Other drug use</td>
</tr>
<tr>
<td>•  Tuberculosis</td>
<td>•  Coronary Artery Disease</td>
</tr>
<tr>
<td>•  Other bacterial infections</td>
<td>•  COPD</td>
</tr>
<tr>
<td>•  Other sexually transmitted infections</td>
<td>•  Hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>•  Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>•  Hypertension</td>
</tr>
<tr>
<td></td>
<td>•  Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>•  Osteoporosis/osteopenia</td>
</tr>
<tr>
<td></td>
<td>•  Non-AIDS malignancies</td>
</tr>
</tbody>
</table>
Case 1

44 year old male with HIV/AIDS, initially diagnosed in 1987, who transferred care to our practice in 2008

- HIV was well-controlled on ART, TDF/FTC and boosted atazanavir
- Other medical problems included osteoporosis, congenital hip dysplasia, hypogonadism, and tobacco use
- Presented for follow-up in September of 2010
- Reported no new symptoms. Denied dysuria, urinary frequency, abdominal pain, or fever.
- Monogamous with one sexual partner
Case 1 - Continued

• Current Medications
  – TDF/FTC 300/200 mg daily
  – Atazanavir 300 mg daily
  – Ritonavir 100 mg daily
  – Oxandrolone 10 mg BID
  – Atorvastatin 20 mg daily
  – Hydrocodone-APAP 5-500 mg prn hip pain
  – Testosterone topical gel daily

• Physical Exam:
  – BP 124/82, P76, Afebrile
  – HEENT, cardiac, lung, and abdominal exams WNL
Case 1 - Continued

Laboratory Findings

– CD4 774 cells/mm³, HIV RNA level < 20 copies/ml
– Cr 1.69 (increased from 1.28 three months prior) with estimated GFR of 44 ml/min/1.73 m²
– Na 146, Cl 111, K 4.7, HCO₃ 26, BUN 18
– Glu 92, AST 36, ALT 40, Alk phos 48, total bili 1.6
– Urinalysis with:
  • Proteinuria (300 mg/dL)
  • Pyuria (> 75 WBCs)
  • Hematuria (> 75 RBCs)
What is the most likely cause for his urinary/renal findings?

A. HIVAN
B. Urinary infection
C. ART toxicity
D. Urolithiasis
E. Renal Cancer
F. Other
Causes of Kidney Disease in HIV-Infected Patients

• HIV-Associated Nephropathy (HIVAN)
• Membranous nephropathy (Hepatitis B, Hepatitis C, and syphilis)
• Membranoproliferative glomerulonephritis (Hepatitis C with mixed cryoglobulinemia)
• Immune complex nephropathy from IgA
• Diabetic and hypertensive nephropathies
• Drug toxicities (e.g. tenofovir, ibuprofen, etc.)
HIV-Associated Nephropathy (HIVAN)

- Azotemia and proteinuria
- Often presenting with nephrotic syndrome
- Seen predominately in blacks
- Evidence of direct HIV invasion
- Often improves on ART
- Pathology: Focal glomerulosclerosis (FSGS)
- Declining in incidence
Fanconi Syndrome

• Fanconi syndrome is a generalized proximal tubulopathy.
• In its complete form, findings include renal tubular acidosis, glycosuria with normoglycemia, aminoaciduria, hypophosphatemia, hypouricemia, and tubular proteinuria.
• Tubular dysfunction may precede the decline of renal function.
• Tubular proteinuria implies the presence in urine of increased amounts of small-sized proteins that are freely filtered in the glomerulus but reabsorbed by proximal tubules.
Tenofovir-Associated Fanconi Syndrome: Review of the FDA Adverse Event Reporting System

- Retrospective review of 164 cases 2001-2006
- 83% of subjects on PIs; 74% of subjects were on boosted PIs
- DDI was the most common other NRTI
- Complications among these patients included hospitalization (46%), fracture (2%), dialysis (2%), and death (2%)

Case 1 – Additional Work-Up

• Urine culture negative
• Screens for Chlamydia and GC negative
• Urine eosinophils negative
• Renal ultrasound: No evidence of renal mass or hydronephrosis. Small focus of hyper echogenicity in the left renal midpole is likely a nonobstructing nephrolithiasis or small angiomyolipoma.
• CT IVP: Small linear calcific density in the lateral midportion of the left kidney may be a small nonobstructive intrarenal calculus or papillary calcification.
• Referred for cystoscopy but never accomplished
# Quantifying Kidney Disease: Our Patient is Stage III

Table 2. Stages of chronic kidney disease.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR, mL/min per 1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>II</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>III</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>IV</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>V</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from [5]. Chronic kidney disease is defined as either kidney damage or glomerular filtration rate (GFR) <60 mL/min per 1.73m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in urine test results or the findings of imaging studies.

Would you stop tenofovir at this time?

A. Yes
B. No
Before Stopping Tenofovir

• Are there other explanations for the patient’s renal findings?
• Are you also treating active Hepatitis B and risking a flare with tenofovir cessation?
• Should the tenofovir be dose-reduced and maintained?
• What are the potential side effects of the proposed new regimen?
Reversibility of Estimated GFR Decline Following TDF Exposure

• United Kingdom HIV Collaborative Cohort
• 3088 (23.7%) of 13,007 patients discontinued TDF therapy; incidence of 7.3/100 person-yrs
• Of the 3088, a decline in eGFR was noted in 1882 (61%) persons
• Following TDF discontinuation, 38.6% of patients did not experience eGFR recovery
• Higher eGFR at baseline, lower eGFR after discontinuation of TDF, and more prolonged TDF exposure were associated with incomplete eGFR recovery

Case 1 - Continued

• Tenofovir discontinued and replaced with raltegravir
• Continued on atazanavir/r and FTC
• Despite this intervention, persistent azotemia and pyuria noted
Case 1 - Conclusion

• Atazanavir changed to darunavir
• Pyuria, proteinuria, and azotemia resolved on this new regimen
Acute Interstitial Nephritis and Nephrolithiasis Due to Atazanavir

• A number of cases of acute interstitial nephritis have been reported in patients on atazanavir\(^1-4\)
• Improvement has been noted with withdrawal of atazanavir
• Nephrolithiasis is also a reported side effect of atazanavir, including 4 cases in the ACTG 5257 trial\(^5\)

\(^5\) Landovitz et al, Abstract 85, 21st CROI, 2014, Boston, MA
Key Reference

Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America*

*An update is in progress.
• A baseline urinalysis and calculated creatinine clearance or estimated glomerular filtration rate should be obtained, especially in black HIV-infected patients and those with advanced disease or comorbid conditions, because of an increased risk of nephropathy (strong recommendation, high quality evidence).

• Urinalysis and calculated creatinine clearance assay should also be performed prior to initiating drugs such as tenofovir or indinavir that have the potential for nephrotoxicity (strong recommendation, moderate quality evidence).
Creatinine Clearance Requirements for Selected Medications and Regimens

- TDF/FTC/cobi/elvitegravir: Creatinine clearance < 70 mL/min
- All other fixed dose combinations, including TDF/FTC, TDF/FTC/RPV, TDF/FTC/EFV, ABC/3TC, and AZT/ABC/3TC either cannot be given or require dose adjustment if creatinine clearance < 50 mL/min
Measurement of Kidney Function Utilizes Serum Creatinine Values

Cockroft-Gault Equation: \( \text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 0.85 \text{ if female}}{72 \times \text{serum creatinine (mg/dL)}} \)

Simplified MDRD Equation: \( \text{GFR (mL/min/1.73m}^2) = 186 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if black}] \)
Which of the following drugs can raise serum creatinine without affecting renal function?

A. Dolutegravir
B. Rilpivirine
C. Cobicistat
D. A and C only
E. All of the above
Drugs that can raise serum creatinine by inhibiting tubular creatinine secretion

<table>
<thead>
<tr>
<th>ARV Agents</th>
<th>Non-ARV Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>Cobicistat</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Pyrimethamine</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Trimethoprim</td>
</tr>
</tbody>
</table>
Effects of ART on Renal Tubular Transporters

Outcomes of Kidney Transplantation in HIV-Infected Recipients

- Prospective, non-randomized trial of kidney transplant in HIV
- Patients with CD4 of at least 200 with an undetectable HIV viral load
- Patient and graft survival compared to Scientific Registry of Transplant Recipients (SRTR cohort)

Case 2

- 45 year old male with long-standing HIV infection and active Hepatitis B, both well controlled on ART
- Other medical problems include cirrhosis with esophageal varices, tobacco use, and COPD
- Referred for unexplained weight loss (40 pounds over 1 year) and wide-spread bone and joint pain (left rib, both hips, both knees, both ankles, and both feet)
Case 2 - Continued

• Current Medications
  – ABC/3TC 600/300 mg daily
  – Atazanavir 300 mg daily
  – Ritonavir 100 mg daily
  – Tenofovir 300 mg daily
  – Aspirin 81 mg daily
  – Fenofibrate 145 mg daily
  – Nadolol 20 mg daily
  – Methocarbamol 500 mg QID
  – Hydrocodone-APAP 5-325 mg every 6 hours prn pain
Case 2 - Continued

- Work-up for malignancy, adrenal insufficiency, and hypothyroidism unremarkable
- Serum testosterone level low at 6.1 ng/dL
- 25-OH vitamin D level low at 15 ng/dL
- CD4 740 cells/mm$^3$, HIV RNA level TND
- MRIs documented severe osteoporosis and evidence of insufficiency fractures of both hips, both femurs and both tibias, and stress fractures involving the calcaneus and other foot bones bilaterally
Key Reference

Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers

Definitions

• **Osteoporosis**: a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Also defined by a T-score $\geq 2.5$ standard deviations below the mean BMD for a healthy, young, sex- and ethnicity-matched reference group.

• **Osteopenia**: a T-score between -1 and -2.49.

• **Osteomalacia**: impaired mineralization of the bone matrix, most often caused by severe vitamin D deficiency.

Low BMD in HIV infection

- Prevalence of osteoporosis may be 3 times higher when compared to general population

- Etiology
  - Untreated HIV infection
  - Presence of traditional risk factors such as tobacco use, alcohol use, androgen deficiency, and Vitamin D deficiency are more common
  - Effects of antiretroviral therapy

In my clinic, I routinely screen my HIV+ patients at age 50 with DXA

A. Yes
B. No
In my clinic, I routinely screen my HIV+ patients for Vitamin D deficiency

A. True
B. False
• Baseline bone densitometry (DXA) screening for osteoporosis in HIV-infected patients should be performed in postmenopausal women and men aged ≥50 years (strong recommendation, moderate quality evidence).

• No guidance regarding screening for Vitamin D deficiency.
Cumulative Use of TDF and/or Boosted PIs and Risk of Osteoporotic Fractures

- Retrospective analysis of 56,660 HIV+ male veterans enrolled from 1988-2009
  - Osteoporotic fractures assessed from ICD-9 codes
- Cumulative use of TDF and/or boosted PI associated with higher risk in ART era, after controlling for risk factors
  - Highest risk with concomitant use
- Cumulative use of LPV/RTV also associated with higher fracture risk
  - PI association limited to LPV/RTV
- Cumulative use of ABC, thymidine analogues, NNRTIs not associated with higher risk

Limitations
- Retrospective cohort study
- BMD data not available
- Fractures not verified to be osteoporotic

ACTG 5202: First-line Therapy With ABC/3TC vs TDF/FTC + EFV vs ATV/RTV

Stratified by HIV-1 RNA < or ≥ 100,000 copies/mL

Antiretroviral-naive patients with HIV-1 RNA ≥ 1000 copies/mL and any CD4+ cell count (N = 1857)

- TDF/FTC* 300/200 mg QD + EFV† 600 mg QD (n = 464)
- ABC/3TC* 600/300 mg QD + EFV† 600 mg QD (n = 465)
- TDF/FTC* 300/200 QD + ATV/RTV† 300/100 mg QD (n = 465)
- ABC/3TC* 600/300 mg QD + ATV/RTV† 300/100 mg QD (n = 463)

Wk 96 primary endpoint


*Double blind.
†Open label.
ACTG 5202: Probability of Virologic Failure at 96 Weeks

P<0.001, log-rank test
Hazard ratio, 2.33 (95% CI, 1.46–3.72)

Metabolic Substudy of ACTG 5202: Lumbar Spine and Hip BMD Changes (ITT)

Comparison of ABC/3TC vs TDF/FTC

- Mean ∆ in BMD From BL to Wk 96 (%): -4.0, -3.0, -2.0, 0
- ABC/3TC: n = 101, 97, 99, 96
- TDF/FTC: n = 107, 91, 105, 90
- Difference: 2.0%

P = .004  P = .025

Comparison of EFV vs ATV/RTV

- Mean ∆ in BMD From BL to Wk 96 (%): -4.0, -3.0, -2.0, 0
- EFV: n = 107, 91, 105, 90
- ATV/RTV: n = 101, 97, 99, 96
- Difference: 1.5%
- Difference: 0.3%

P = .035  P = .59

- Initial loss in BMD in all arms stabilized after Wk 48
- No significant differences in fracture rates between arms

ACTG 5257: Open-Label ATV/RTV vs RAL vs DRV/RTV in First-line ART

ART-naive patients with HIV-1 RNA \( \geq 1000 \text{ c/mL} \) (\( N = 1809 \))

- Primary endpoints
  - **Virologic failure**: time to HIV-1 RNA > 1000 c/mL (at Wk 16 or before Wk 24) or > 200 c/mL (at or after Wk 24)
  - **Tolerability failure**: time to discontinuation of randomized component for toxicity

Results: Raltegravir arm superior to the darunavir arm. Darunavir arm superior to the atazanavir arm.

Landovitz et al, Abstract 85, 21st CROI, 2014, Boston, MA
ACTG 5257: Loss of BMD With First-line Boosted PI vs RAL

- All arms associated with significant loss of BMD through Week 96 \((P < .001)\)
- Total body BMD loss significantly greater with ATV/RTV than either DRV/RTV or RAL
- At hip and spine, similar loss of BMD in the PI arms
  - Significantly greater loss in the combined PI arms than in the RAL arm

Case 2: Dual Energy X-ray Absorptiometry (DXA) Results

<table>
<thead>
<tr>
<th>Site</th>
<th>T-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1-4</td>
<td>-3.0 STD</td>
</tr>
<tr>
<td>Left femoral neck</td>
<td>-5.4 STD</td>
</tr>
<tr>
<td>Left femur total</td>
<td>-5.0 STD</td>
</tr>
<tr>
<td>Right femoral neck</td>
<td>-5.8 STD</td>
</tr>
<tr>
<td>Right femur total</td>
<td>-5.6 STD</td>
</tr>
</tbody>
</table>
Who should receive treatment for osteoporosis?

• Post-menopausal women and men > 50 years with T score of the total hip, femoral neck, or lumbar spine ≤ 2.5

• Patients with a history of a fragility fracture

Pharmacologic Treatment of Osteoporosis

• First-line therapies are the biphosphonates (alendronate, risedronate, ibandronate, and zoledrendenic acid)

• Second-line therapies can include estrogen-replacement therapy (risks noted), intranasal calcitonin, and teriparatide (an analogue of PTH)

• Antiretroviral switch is also an option

Case 2 - Continued

• Treatment included vitamin D and calcium supplementation
• Placed on alendronate
• Follow up DXA testing 1 year later demonstrated progression of his osteoporosis
• Repeat MR imaging with new fractures involving femur and multiple foot bones
Would you stop tenofovir at this time?

A. Yes
B. No
Case 2 - Conclusion

- Seen by Endocrinology.
- Alendronate discontinue.
- Placed on teriparatide.
- TDF maintained given chronic Hepatitis B and risk for flare if stopped.
General Guidelines for Bone Health

• Calcium 1000-1500 mg daily
• Vitamin D 800-1000 IU daily
• Smoking cessation
• Limitation of alcohol intake
• 30 minutes of weight-bearing exercise TIW
• Evaluate for secondary causes including Vitamin D deficiency and phosphate wasting related to TDF use

ACTG 5280: High-Dose Vitamin D and Calcium Attenuate Bone Loss

- Randomized, double-blind trial in pts initiating TDF/FTC/EFV with baseline vitamin D 10-75 ng/mL
  - Vitamin D3 4000 IU/day plus
  - Calcium carbonate 1000 IU/day
- Significant, 50% reduction in loss of hip BMD at Wk 48 in treated pts
- Smaller nonsignificant difference in spine BMD in treated pts
- Smaller increase in markers of bone turnover in treated pts

Decline in BMD From Baseline to Wk 48

Change in BMD (%)

Vitamin D/calcium | Placebo
---|---
Total Hip: -1.46 | -3.19
Lumbar Spine: -1.41 | -2.91

Lower and upper edges of box indicate 25th and 75th percentiles; lines inside box indicate median.

## Recommended Initial Antiretroviral Regimens

<table>
<thead>
<tr>
<th>NNRTI-based regimens</th>
<th>2014 DHHS Guidelines¹</th>
<th>2014 IAS-USA Guidelines²</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Efavirenz/TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI-based regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Atazanavir/r plus TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Darunavir/r plus TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSTI-based regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dolutegravir plus ABC/3TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dolutegravir plus TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Elvitegravir/cobi/TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Raltegravir plus TDF/FTC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tenofovir Alafenamide (TAF, GS-7340)

Tenofovir

Tenofovir Disoproxil Fumarate

Tenofovir Alafenamide

Gut
- TFV
- TDF
- TAF

Plasma
- TDF → TDF/TFV
- TAF → TAF

Lymphoid Cells
- TAF → TFV
- TFV
- TFV-MP
- TFV-DP

Cathepsin A
TAF/FTC/EVG/COBI Non-inferior to TDF/FTC/EVG/COBI Through Week 48 with Less Bone and Renal Toxicity

- TAF: lower plasma levels, higher PBMC levels
- Randomized (2:1), double-blind phase II trial
- 112 in TAF arm, 58 in TDF arm
- 48 week data presented
- Less bone and renal toxicity in the TAF arm

HIV VL < 50 at 48 weeks

Patients on TAF had smaller decrease in eGFR
- -5.5 vs -10.0 mL/min with TDF ($P = .041$)
- No renal discontinuations and no tubulopathy in either arm
- Less change in renal tubular proteins with TAF

Smaller change in both spine and hip BMD (by DXA) over 48 wks with TAF vs TDF

Current Status of TAF

• Remains investigational
• Currently in Phase III development
• Products in development include several fixed-dose combinations:
  – TAF/FTC/cobicistat/elvitegravir
  – TAF/FTC/cobicistat/darunavir
  – TAF/FTC
Summary

1. CKD and Osteoporosis are common in HIV infection and can be related to HIV itself, co-morbidities, or the effects of ART.

2. Screening and aggressive treatment of these complications may minimize their impact.

3. The most commonly prescribed antiretroviral agent, tenofovir DF, can produce both CKD and osteoporosis.

4. Safer therapies may be on the horizon.