

**20<sup>th</sup> ANNUAL HIV CONFERENCE**  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Complications of Antiretroviral Therapy

Sandy J. Estrada, Pharm.D., BCPS  
Lee Memorial Health System

### Disclosure of Financial Relationships

**This speaker has no significant financial relationships with commercial entities to disclose.**

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.



**20<sup>th</sup> ANNUAL HIV CONFERENCE**  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Objectives

- Discuss the most common and most severe potential complications of antiretroviral therapy
- Present cases to demonstrate complications of therapy
- Discuss monitoring to minimize the risk of antiretroviral complications



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Currently Recommended 1<sup>st</sup> line therapies

- Efavirenz/Tenofovir/Emtricitabine
- Atazanavir/ritonavir+Tenofovir/Emtricitabine
- Darunavir/ritonavir+ Tenofovir/Emtricitabine
- Raltegravir + Tenofovir/Emtricitabine

US DHHS Guidelines; Revised Jan 10, 2011



May 13-14, 2011  
Orlando, FL

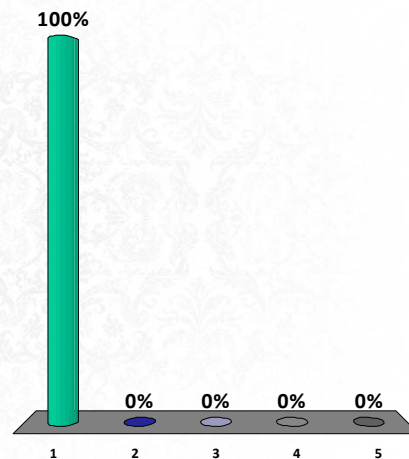
[www.FCAETC.org](http://www.FCAETC.org)

# Case 1

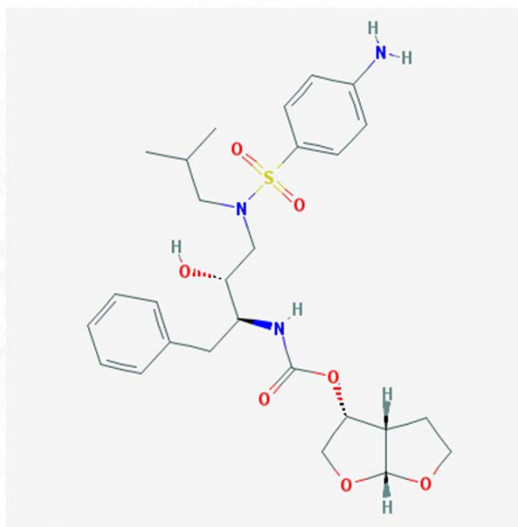
- 40 y/o female admitted May 2009 with possible recurrence of Steven-Johnson Syndrome (SJS)
- **Current Medications:**
  - Darunavir/ritonavir + Emtricitabine/tenofovir
  - Atovaquone
  - Escitalopram
  - Amlodipine
  - Lantus insulin
  - Levothyroxine
  - Pravastatin
- **Allergies: Trimethoprim/Sulfamethoxazole – caused SJS (1/09)**

## Which medication is most likely the cause of this patient's SJS?

1. Emtricitabine
2. Tenofovir
3. **Darunavir**
4. Ritonavir
5. Non-ART medication



## Darunavir



ANNUAL  
HIV CONFERENCE  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Case 2

- 39 y/o male presents to hospital ER with HIV since 2009, severe wasting and esophagitis
- ART: atazanavir/ritonavir + emtricitabine/tenofovir
- Urinalysis on admission: shows 100+ protein, 250+ glucose, otherwise normal
- Serum creatinine elevated at 1.23 mg/dl (baseline 0.5)



ANNUAL  
HIV CONFERENCE  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Case 2

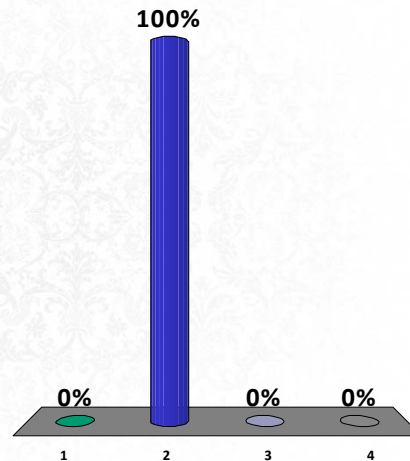
- **Meds on Admission**
  - Atovaquone
  - Clarithromycin
  - Dronabinol
  - Sertraline
  - Isoniazid
  - Ethambutol
  - Megesterol
  - Gabapentin

## Case 2

- **Nephrology consult: Metabolic acidosis, suspect drug toxicity due to Fanconi's syndrome**
  - Check serum phosphorus: 1.9 mg/dl

## Which medication is the most likely cause of Fanconi's syndrome

1. Ritonavir
2. Atazanavir
3. **Tenofovir**
4. Emtricitabine



ANNUAL  
HIV CONFERENCE  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Fanconi's Syndrome

- Defect in proximal tubule transport characterized by renal tubular acidosis, glucosuria, aminoaciduria, proteinuria, phosphaturia, hypophosphatemia, uricuria and hypouricemia
- Osteomalacia and Rickets as secondary consequences



ANNUAL  
HIV CONFERENCE  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Tenofovir and Nephrotoxicity

- **Tenofovir structurally related other medications known to cause nephrotoxicity**
  - Cidofovir
  - Adefovir
- **Tenofovir reports of nephrotoxicity in clinical trials and literature are rare**



**ANNUAL  
HIV CONFERENCE**  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Tenofovir Nephrotoxicity

- **744 patients on tenofovir > 3 months with baseline serum creatinine**
- **191 patients not on tenofovir**
- **Nephrotoxicity defined as a decrease of 50% or more in GFR or a 25 ml/min decrease in creatinine clearance**

C Castellano, W Williams, TB Kepler, and others. Clinical predictors of tenofovir-associated nephrotoxicity in HIV-1-infected patients. XVII International AIDS Conference (AIDS 2008). Mexico City. August 3-8, 2008. Abstract WEAB0104.



**ANNUAL  
HIV CONFERENCE**  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Tenofovir Nephrotoxicity

- 35 of 744 patients taking tenofovir developed nephrotoxicity (4.7%)
- 8 of 191 control patients developed nephrotoxicity (4.2%)
- Kidney function improved in 16/20 patients who discontinued tenofovir (80%)
- 10/15 patients who stayed on tenofovir had persistently abnormal kidney function

C Castellano, W Williams, TB Kepler, and others. Clinical predictors of tenofovir-associated nephrotoxicity in HIV-1-infected patients. XVII International AIDS Conference (AIDS 2008). Mexico City. August 3-8, 2008. Abstract WEAB0104.



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Tenofovir Nephrotoxicity

- Significant independent predictors of developing nephrotoxicity
- Use of tenofovir as part of an HAART initial regimen was associated with diminished risk of nephrotoxicity

Condition	Odds Ratio
History of opportunistic infection	2.4
Previous protease inhibitor	2.8
Current PI Use	3.79
Chronic Pain	4.58
Hypertension	4.79
Medical co-morbidities	5.43
Concurrent nephrotoxic medications	6.36

C Castellano, W Williams, TB Kepler, and others. Clinical predictors of tenofovir-associated nephrotoxicity in HIV-1-infected patients. XVII International AIDS Conference (AIDS 2008). Mexico City. August 3-8, 2008. Abstract WEAB0104.

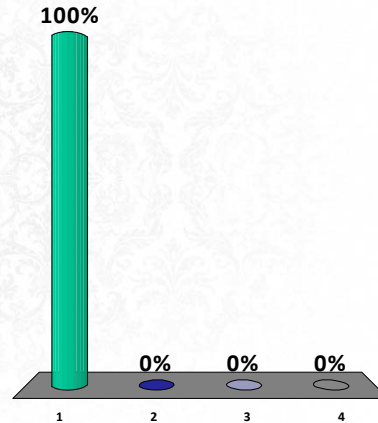


May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

**What is the proper tenofovir dose for a patient with an estimated creatinine clearance of 40 mL/min?**

1. 300 mg daily
2. 300 mg q48hrs
3. 150 mg daily
4. Don't use tenofovir in this patient population

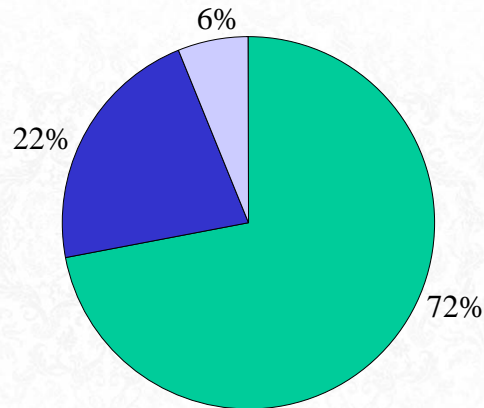


## Tenofovir Renal Dosing

>50 mL/min	30-49 mL/min	10-29 mL/min	Hemodialysis
300 mg every 24 hours	300 mg every 48 hours	300 mg every 72-96 hours	Every 7 days or after a total of approximately 12 hours of dialysis

Tenofovir Prescribing Information. October 2010.

## Consistency of Tenofovir Renal Adjustment



■ Dosed higher ■ Dosed as Recommended ■ Dosed lower

Phillips B et al., 15<sup>th</sup> CROI 2008. abstract 757



ANNUAL  
HIV CONFERENCE

of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

www.FCAETC.org

## Tenofovir - Monitoring

- **At baseline**
  - Serum creatinine
  - Calculated creatinine clearance
  - Urinalysis for protein
- **Follow-up**
  - Serum creatinine and urinalysis
    - Every 6 months if normal baseline
    - More frequently if clinically warranted

US DHHS Guidelines; Revised Jan 10, 2011



ANNUAL  
HIV CONFERENCE

of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

www.FCAETC.org

## Tenofovir - Monitoring

- **What patients should not take tenofovir?**
- **If no tenofovir – what do we use:**
  - Abacavir/Lamivudine
  - Zidovudine/Lamivudine

US DHHS Guidelines; Revised Jan 10, 2011



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

**Does abacavir use increase  
the risk of MI?**



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## D:A:D Study: Impact of Select NRTIs on Risk of MI in HIV-Infected Patients

- Data on 33,347 HIV infected patients on ART
- Increased risk for Abacavir compared with certain other NRTIs
  - RR 1.16 (95% CI: 1.1-1.23) for MI per additional year of exposure to combination ART
- TDF data not included in initial analysis, but were added at a subsequent analysis

D:A:D Study Group. Lancet. 2008;371:1417-1426.  
Worm et al. JID. 2010;201:318-330



ANNUAL  
HIV CONFERENCE

of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

www.FCAETC.org

## FDA Meta-Analysis

- Presented at CROI 2011
- Meta-analysis of 26 randomized controlled trials involving ABC
  - 5028 subjects on ABC
  - 4840 controls
  - Average 1.62 years follow-up
  - Overall events/subjects:
    - 28/5628 ABC vs 22/4840 controls (OR 1.02 95% CI 0.56, 1.84)
  - Findings “raise significant uncertainty about the likelihood of ABC-MI risk association”

Ding X et al. 18<sup>th</sup> CROI; Boston, MA; Abstract 808



ANNUAL  
HIV CONFERENCE

of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

www.FCAETC.org

## Abacavir Cardiotoxicity

- **Current Conclusion:**
  - Use with caution in patients with risk factors for cardiovascular disease
- **Other Abacavir Cautions**
  - HLA-B\*5701 testing should precede the use of abacavir to reduce risk of hypersensitivity syndrome
  - Less activity compared to tenofovir in patients with high VL (>100,000 c/ml)

US DHHS Guidelines; Revised Jan 10, 2011



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Case 3

- **23 year old male newly diagnosed with HIV in April 2010**
- **VL: 21, 900 c/ml**
- **CD4: 8**
- **NKDA or other contraindications to therapy**
- **Baseline genotype: no ART resistance**
- **Started on Efavirenz/Emtricitabine/Tenofovir 1 tablet daily at bedtime**



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Case 3

- Returns to clinic for follow-up June 2010
- Not friendly with office staff, refusing to answer questions, only wishes to speak with physician
- Upon interview with physician states hasn't been sleeping well due to bad dreams



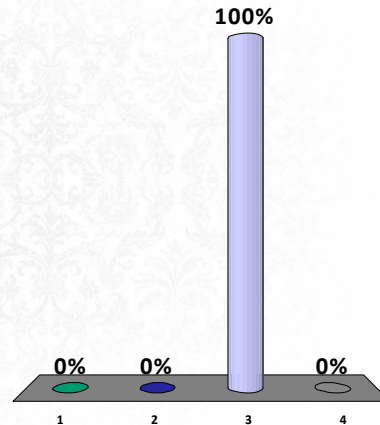
ANNUAL  
HIV CONFERENCE  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

www.FCAETC.org

Which medication might be the cause of the sleep disturbance/mood change?

1. **Efavirenz**
2. Tenofovir
3. Emtricitabine
4. Not medication related



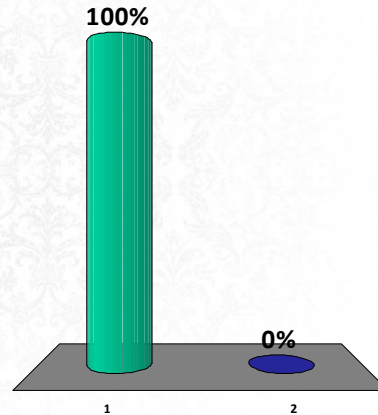
ANNUAL  
HIV CONFERENCE  
of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

www.FCAETC.org

## Would you change this patient's ART ?

- 1. Yes
- 2. No



## Efavirenz

- **Adverse Effects**
  - Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation

## Efavirenz Monitoring

- **Risk factors for development of CNS side effects**
  - History of psychiatric illness
  - Concomitant use of agents with neuropsychiatric effects
  - Increased plasma concentrations due to genetic factors or absorption
- **Most symptoms subside or diminish after 2-4 weeks**



ANNUAL  
HIV CONFERENCE

of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Other Antiretroviral Complications

- **Bone Marrow Suppression**
  - Zidovudine
- **Dyslipidemia**
  - All ritonavir boosted PIs
  - Efavirenz
  - Stavudine>Zidovudine>Abacavir
- **GI Intolerance**
  - NRTIs and PIs

US DHHS Guidelines; Revised Jan 10, 2011



ANNUAL  
HIV CONFERENCE

of the Florida/Caribbean  
AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Other Antiretroviral Complications

- **Hepatic effects**
  - Possible with all NRTIs and Protease Inhibitors
  - NNRTIs-Largest incidence with nevirapine
    - Usually associated with hypersensitivity rash
    - Women at higher risk
    - High CD4 count = higher risk
      - >250 in women
      - >400 in men
    - 2 week dose escalation reduces risk
    - Nevirapine should never be used for post exposure prophylaxis

US DHHS Guidelines; Revised Jan 10, 2011



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Other Antiretroviral Complications

- **Lactic acidosis**
  - NRTIs
    - Higher with Stavudine, Didanosine and Zidovudine
    - Increase risk: female, obesity
- **Osteopenia/Osteoporosis**
  - Associated with all NRTI, NNRTI and PI therapy
    - Risk may be higher with tenofovir vs other NRTIs

US DHHS Guidelines; Revised Jan 10, 2011



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## What about Raltegravir?

- GI Intolerance
- Pyrexia
- CPK elevations
  - Muscle weakness/rhabodmyolysis

US DHHS Guidelines; Revised Jan 10, 2011



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

# Questions?



May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)

## Disclosure of Financial Relationships

**This speaker has no significant financial relationships with commercial entities to disclose.**

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.



**ANNUAL  
HIV CONFERENCE**

*of the Florida/Caribbean  
AIDS Education and Training Center*

May 13-14, 2011  
Orlando, FL

[www.FCAETC.org](http://www.FCAETC.org)