

**18th Annual  
HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center

**May 1-2, 2009**  
Orlando, FL

# Complications of Antiretroviral Therapy

**Jose A. Montero MD, FACP**  
**Faculty Florida/Caribbean AETC**  
**Associate Professor of Medicine**  
**Division of Infectious Diseases**  
**University of South Florida College of Medicine**



## Disclosure of Financial Relationships

**This speaker has the following significant financial relationships  
with commercial entities to disclose:**

- **This speaker has received research support from Pfizer.**

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

**18th Annual  
HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center

May 1-2, 2009 • Orlando, FL

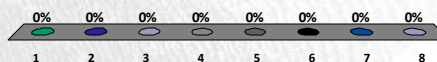
## Objectives

- Discuss the common adverse effects seen in patients receiving antiretroviral agents
- Discuss the proposed mechanisms of these adverse drug effects
- Assist the clinician in ways to provide early diagnosis of these adverse drug effects
- Highlight the management strategies in patients who experience these adverse effects

18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Who is in Our Audience?

1. Dentist / Dental Professional
2. Nurse Practitioner / Physician Assistant
3. Nurse
4. Pharmacist / PharmD
5. Physician
6. Case Manager
7. Mental Health or Substance Abuse Professional
8. Other



18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Antiretroviral Agents

- **NRTIs (nucleosides/nucleotides)**
- **NNRTIs (non-nucleosides)**
- **PIs (protease inhibitors)**
- **Fusion Inhibitor**
- **Chemokine Receptor Inhibitor**
- **Integrase Inhibitor**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Common Adverse Effects of ARV

- **Hepatotoxicity**
- **Hyperlipidemia**
- **Lipodystrophy**
- **Diabetes Mellitus / Insulin Resistance**
- **Lactic Acidosis**
- **Pancreatitis**
- **Peripheral Neuropathy**
- **Others (BM suppression, osteopenia, rash, etc.)**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Hepatotoxicity

- **Defined as serum transaminases greater than 3 to 5 times upper limit of normal**
- **All ARV classes have been implicated**
  - Can occur at any time with PIs, but usually early
  - Seen from weeks to few months in NNRTIs
  - Many take many months in NRTIs
    - May be associated with hepatic steatosis and lactic acidosis
- **Risk factors**
  - Hepatitis B or C co-infection
  - Alcoholism
  - Baseline elevated AST or ALT
  - Concomitant use of other hepatotoxic agents

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Nevirapine Hepatotoxicity

- **Generally seen within 1<sup>st</sup> 12-18 weeks of use**
- **About half who are symptomatic also have a rash**
- **Host factors include:**
  - Women (3 times more than men)
  - CD4>250 in women, CD4>400 men
  - HIV (-) used in post-exposure prophylaxis
- **Monitor liver enzymes closely in the 1st 3 months of use**
  - At 2 and 4 weeks, then monthly for first 3 months, then every 3 months
  - If rash with nevirapine, also check liver enzymes
- **Do not re-challenge**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Management of Hepatotoxicity

- **Rule of other causes**
  - Viral Hepatitis or rebound of Hepatitis B
  - Alcoholism
  - Concomitant medications
- **If symptomatic, discontinue all ARV and possible hepatotoxic drugs. Then restart new ARV with least hepatotoxic potential.**
- **If asymptomatic, many would consider discontinuing ARV at 5-10 times ULN. Then restart with new ARV when liver enzymes normalize.**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Cuba AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Hyperlipidemia

- **Elevation of triglycerides(TG), cholesterol(TC), LDL**
- **Onset usually weeks to months after ARV**
- **All PI's except unboosted atazanavir**
  - ATV/r slightly less TG and LDL than other RTV-boosted PIs
  - Disproportionate high TG in LPV/r and FPV/r
- **NNRTI: EFV>NVP see high LDL and TC**
- **NRTI: d4T>ZDV>ABC>TDF**
  - High TG, TC, LDL
- **Some boosted PIs and NNRTIs also raise HDL**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Cuba AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Management of Hyperlipidemia

- **Assess cardiac disease risk factors when considering ARV regimens**
- **Lifestyle modification:**
  - Diet
  - Exercise
  - Smoking cessation
- **Can switch to ARV agents with less lipid effect**
- **Pharmacologic management**
  - Careful with drug interactions with “statins”

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

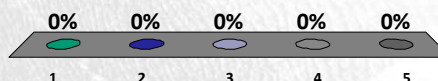
## Case

35 year old HIV+ male who recently started ARV consisting of tenofovir / emtricitabine / lopinavir (rit-boosted) 6 months ago. His CD4 has risen from 270 to 390 and his HIV viral load has become undetectable (<50 copies/ml). However his fasting serum cholesterol now is 310 (<200), LDL is 140 (<100), and triglycerides are 170 (<150) despite adequate dietary and exercise interventions. What is his best treatment option in this patient who does not want to change his ARV?

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Case (Best treatment option)

1. Change his ARV to lipid friendly regimen
2. Pravastatin
3. Lovastatin
4. Gemfibrozil
5. Simvastatin



18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Cardiovascular Effects

- To some degree MI and CVA risk linked to hyperlipidemia
- Add traditional risk factors
- Observational cohort found possible association of ABC and ddl use and MI in patients at high cardiovascular risk\*
- With longevity of HIV-infected due to ARV, must now provide early diagnosis, prevention, and management

18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

\* DAD Study Group. Lancet, 2008; 1417-26

# Lipodystrophy

## Lipoatrophy

- Peripheral fat loss
- Facial thinning
- Thinning of extremities
- NRTI (d4T>ZDV>other NRTI)

## Lipohypertrophy

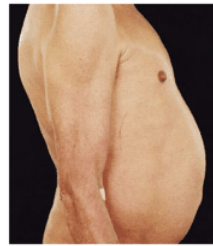
- Increase abdominal girth
- Increase breast size
- Buffalo hump (dorsocervical fat pad)
- PI or NNRTI agents with d4T or ZDV

18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

# Lipodystrophy



Dorsocervical fat pad  
Aka "Buffalo Hump"



Central Obesity

18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

Carr and Cooper: New Eng J Med 339, 1296

## Facial Wasting



18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

Hendi, et al. Lipodystrophy, HIV.  
[www.emedicine.com](http://www.emedicine.com)

## Lipodystrophy

- **Exact etiology not known**
- **Treatment options**
  - Switch ARV may slow or halt progression but not fully reverse effects
  - Recombinant growth hormone?
  - Cosmetic procedures
    - Injectable fillers for facial lipoatrophy (e.g. Sculptra®)
    - Liposuction or surgical removal of buffalo hump

18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Diabetes Mellitus / Insulin Resistance

- Seen more commonly in those taking d4T, ZDV, and some PIs
- Risk factors include family history of DM
- Treatment:
  - Can consider switching ARV
  - Diet and exercise
  - Pharmacotherapeutic management

18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Monitoring of ARV Side Effects

### Fasting Lipids

- Annually if off ARV and normal
- At ARV initiation/switch
- Consider at 2-8 wks after ARV initiation/switch
- Every 6 months if borderline or abnormal at last reading on ARV
- Annually if normal on ARV

### Fasting Glucose

- Annually if off ARV and normal
- At ARV initiation/switch
- Every 3-6 months if borderline or abnormal at last reading on ARV
- Every 6 months if normal on ARV

18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. DHHS. Nov 3, 2008;1-139. Table 3

## Lactic Acidosis

- **Mechanism of disease is through disruption of DNA polymerase gamma in mitochondria by certain NRTI's (d4T, ddl, ZDV)**
- **Results in lactic acidosis and hepatic steatosis**
- **Mortality very high if serum lactate > 10mmol/L**
- **Risk Factors include:**
  - Long use of d4T, ddl, ZDV
  - Female gender
  - Pregnancy
  - Obesity

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Lactic Acidosis

- **Symptoms include:**
  - Insidious onset of nonspecific GI prodrome
  - Then rapid tachycardia, tachypnea, jaundice, muscular weakness, and mental status change
  - Pancreatitis and multisystem organ failure can occur
- **Lab findings include:**
  - Increased serum lactate
  - Increased anion gap
  - Elevated transaminases
  - Elevated amylase and lipase if pancreatitis present
- **Routine screening of lactic acid not recommended**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Management After Lactic Acidosis

- **If mild, switch ARV**
- **If severe, stop ARV until resolution, then switch**
  - Consider NRTI-sparing regimen or NRTI with less propensity for mitochondrial toxicity
  - Monitor serum lactate if restarting NRTI
- **Symptomatic support during lactic acidosis**
  - thiamine or riboflavin?

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Pancreatitis

- **Risk factor includes**
  - ddI use alone or ddI + d4T or TDF (without dose adjustment)
  - History of pancreatitis
  - Alcoholism
  - Hypertriglyceridemia
- **Routine monitoring of amylase and lipase not recommended**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Peripheral Neuropathy

- Associated with ddl, d4T, ddC use
- Usually seen within weeks to months of therapy
- Begins with numbness & paresthesia of toes and feet
- May progress to painful neuropathy
- Can be very debilitating and relatively irreversible or long-lasting

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Peripheral Neuropathy

- **Risk Factors:**
  - Pre-existing peripheral neuropathy
  - Combination of offending agents
  - Advanced HIV disease
- **Treatment options:**
  - Discontinue offending agent and switch therapy
  - Pharmacologic management
    - Gabapentin, tricyclic antidepressants, lamotrigine, oxcarbazepine, topiramate, tramadol
    - Narcotic analgesics
    - Topical capsaicin or lidocaine

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## **Dermatologic Reactions**

- **Rash common with nevirapine especially if 2 week lead in with 200mg daily not done**
- **Rare is Stevens-Johnson Syndrome or TEN**
  - Very rare reports with a variety of agents but highest rate with nevirapine (0.3%-1%)
  - Skin eruption with mucosal involvement
  - Blister, then bullae, then sloughing
- **Treatment involves removing any offending agent and possible hospitalization if TEN**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## **Dermatologic Reactions**

- **Case reports of TEN and rashes have been seen with other agents including abacavir, didanosine, zidovudine, fosamprenavir, lopinavir, indinavir, atazanavir**
- **Protease inhibitors with sulfa moiety**
  - Use with caution but not contraindicated in those who are sulfa allergic
    - Fosamprenavir
    - Tipranavir
    - Darunavir

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Efavirenz Related CNS Effects

- Very commonly can cause drowsiness, somnolence, insomnia, abnormal dreams, dizziness, and impaired concentration
- Can exacerbate psychiatric disorders, psychosis, depression, and suicidal ideation
- Onset early within 1<sup>st</sup> few doses and typically subside or diminish in 2 to 4 weeks
- Avoid use in at risk population
- Take at or near bedtime and on empty stomach
- Warn patients and suggest low risk activities in 1<sup>st</sup> few weeks

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Case

35 year old HIV+ male who has been taking tenofovir / emtricitabine / fosamprenavir(rit-boosted) for the past 6 months without any side effects until the last 5 weeks when he began to experience excessive thirst and urination with mild nausea and 10lb weight loss. Physical exam revealed a very thin male with dry mucous membranes. Otherwise normal exam.

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

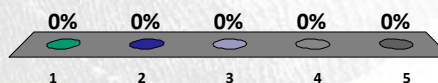
## Case

- **Labs:**
  - UA: (+) glucose, (+) protein, specific gravity 1.004
  - CMP (non-fasting):
    - Chloride 112 (100-108)
    - Bicarbonate 16 (22-29) ; non-anion gap
    - Creatinine 1.9 (0.8-1.3)
    - Glucose 103 (70-100)
    - Phosphorus 1.6 (2.5-4.5)
    - Uric acid 1.9 (3.7-8.0)
  - Urine osmolality 202 (300-800)

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## What should be done next for this patient?

1. **Stop ritonavir boosted fosamprenavir**
2. **Stop tenofovir**
3. **HbA1C**
4. **Renal ultrasound**
5. **Head CT/MRI**



*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Tenofovir Related Nephrotoxicity

- **Can occur weeks to months after use**
- **Fanconi Syndrome**
  - Type 2 or proximal renal tubular acidosis
  - Hypophosphatemia, proteinuria, glycosuria
- **Can advance to nephrogenic diabetes insipidus and renal failure in few individuals**
- **Use with care if other nephrotoxic agents are used, prior history of renal disease, and in those with advanced age**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Tenofovir Related Nephrotoxicity

- **Monitor for toxicity**
  - Serum creatinine, potassium, and phosphorus
  - Urinalysis
- **Treatment**
  - Stop tenofovir
  - Generally reversible if identified early

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

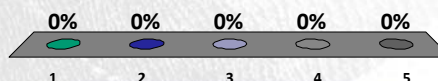
## Case

32 year old white female with HIV and mild renal insufficiency was begun on ARV consisting of Epzicom (abacavir + lamivudine) and Kaletra. One month into therapy she has a HIV viral load of 250 (baseline 90,000) and CD4 count of 335. She complains of a macular rash, myalgias, fever, and nausea. She does not complain of any respiratory symptoms. What is the most likely cause?

18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Case (Most likely cause:)

1. Kaletra
2. IRIS (Immune Reconstitution Inflammatory Syndrome)
3. Abacavir
4. An opportunistic infection
5. Hepatitis B flare



18th Annual  
HIV CONFERENCE  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## **Abacavir Related Hypersensitivity Reaction**

- **Onset usually by 6 weeks (median 9 days)**
- **Combination of symptoms (usually >2-3):**
  - High fever / Chills
  - Diffuse skin rash
  - Malaise
  - Nausea / Vomiting
  - Headache
  - Myalgias / Arthralgias
  - Diarrhea / Abdominal discomfort
  - Dyspnea / Tachypnea

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## **Abacavir HSR**

- **Clinically suspected in ~5-8% in clinical trials**
- **Significantly reduced with HLA-B\*5701 screen**
- **If (+) HLA-B\*5701 screen, then label as allergic**
- **Rare cases seen of HSR in those (-) to screen**
- **Educate patients of symptoms to look for**
- **Treat by discontinuing ABC**
- **Never re-challenge**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Other Drug Specific Reactions

- **Indinavir**      nephrolithiasis, hyperbilirubinemia
- **Atazanavir**    hyperbilirubinemia
- **Nelfinavir**     diarrhea
- **Tipranavir**     intracranial hemorrhage
- **Zidovudine**     bone marrow suppression

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Osteopenia / Osteoporosis

- **Osteopenia** – DEXA t-score 1-2.5 SD from normal
- **Osteoporosis** – DEXA T-score > SD 2.5 from normal
- **Seen with variety of ARV but evidence accumulating with use of TDF > d4T**
- **Usually takes month to years to occur**
- **Asymptomatic but increases risk of fractures**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Osteopenia / Osteoporosis

- **Consider screening with DEXA scan**
  - Proper interval not established for HIV patients
- **Treatment options:**
  - Stop TDF and d4T
  - Weight-bearing exercise
  - Calcium and vitamin D supplementation
  - Alcohol and smoking cessation
  - Bisphosphonates
  - Intranasal calcitonin
  - Judicious hormone replacement

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## Antiretroviral Medications

- **Are “Life Saving” medications for HIV +**
  - Dramatic improvement in quality of life and life expectancy
  - Newer medications have reduced pill burden and generally with better tolerability
- **However, no medication is without its side effects or possible complications**

**Be “armed” with knowledge of HIV medications**

*18th Annual*  
**HIV CONFERENCE**  
of the Florida/Caribbean AIDS Education and Training Center  
May 1-2, 2009 • Orlando, FL

## For More Information

- **Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (Nov. 3, 2008)**
  - <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>
- **AIDS Info: Side Effects of Anti-HIV Medications (patient brochures, Oct. 2005)**
  - [http://aidsinfo.nih.gov/contentfiles/SideEffectAnitHIVMeds\\_cbrochure\\_en.pdf](http://aidsinfo.nih.gov/contentfiles/SideEffectAnitHIVMeds_cbrochure_en.pdf)