
 **19th Annual HIV CONFERENCE**
May 14-15, 2010 • Orlando, FL

Complications of Antiretrovirals


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Disclosure of Financial Relationships

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with commercial entities to disclose.**

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Lecture Objectives

- **Upon completion of this lecture the participant should be able to:**
 - Answer questions relative to complications associated with the use of antiretroviral agents
 - Discuss the mechanisms involved with the complications identified and,
 - Discuss how to prevent and manage complications associated with the use of these medications



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Factors to Consider Concerning ARV Adverse Drug Reactions

- **Understanding the Importance of Black Box Warnings**
- **Identify common adverse effects for each medication and monitor patient appropriately at each visit**
- **Understand the role of drug elimination to avoid drug accumulation to avoid the development of adverse drug effects**
- **Order necessary laboratory tests to prevent or detect adverse effects when possible**



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Nucleoside Reverse Transcriptase Inhibitors (NRTIs)



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Case 1

- RR is a 57 yo bf seen in your clinic today c/o extreme fatigue, increased temperature (102°-103°F) x 5 days.
- Current meds:
 - Combivir® (zidovudine/lamivudine) 1 tab PO bid x 6 weeks, Kaletra® 200/50mg (lopinavir/ritonavir) 2 tabs PO bid x 6 weeks, Septra DS® (sulfamethoxazole/trimethoprim) 1 tab PO q MWF
- Wt 105 lbs, ht 5'7", serum creatinine 1.1 mg/dL, electrolytes normal, current HIV RNA <48, CD4 count is 200

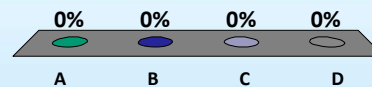


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Which labs should be ordered to determine if drug-related complications exist?

- A. Serum potassium**
- B. Serum bicarbonate**
- C. CBC with differential**
- D. HLA-B*5701**



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Discussion Points

- Zidovudine (Retrovir®) may cause bone marrow suppression within the first few weeks to months after initiating therapy
- CBC with differential will allow the clinician to determine evidence of bone marrow suppression (total WBC, differential, Hgb, Hct)
- Severe anemia (Hgb < 7gm/dl) and severe neutropenia (ANC < 500 cells/mm³) can occur

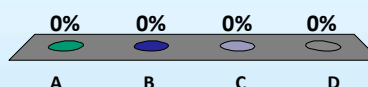


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Risk factors predisposing patients for bone marrow toxicity include?

- A. Concurrent administration of Bactrim DS[®] (sulfamethoxazole/trimethoprim) and zidovudine (Retrovir[®])
- B. Pre-existing anemia or neutropenia
- C. Advanced AIDS
- D. All of the above

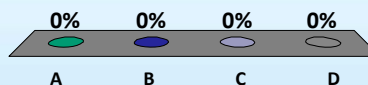


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Truvada[®] (emtricitabine/tenofovir) was ordered for the patient on the previous slide (CrCl = 42.52 mL/min).
What dosing should be used?

- A. 1 tablet daily
- B. 1 tablet every 48 hours
- C. 1 tablet every 72 hours
- D. 1 tablet every 96 hours



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Discussion Points

- **Tenofovir may cause nephrotoxicity**
- **Calculate creatinine clearance for patients receiving tenofovir to avoid accumulation**
- **If creatinine clearance is greater than 49ml/min, one tablet daily is administered**
- **If creatinine clearance is between 30-49 ml/min, the dosing interval should be changed to every 48 hours**
- **If creatinine clearance is less than 30ml/min, avoid use**



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Case 2

- **A patient in your clinic has been diagnosed with HIV infection and the Provider has ordered Epzicom[®] (abacavir/lamivudine) one tablet PO every day and Sustiva[®] (efavirenz) 600mg qHS**
- **Two weeks later, the patient informs you that he had a rash and stopped taking the medication. He restarted both meds two days ago and is experiencing an elevated temperature, diffuse rash and myalgia**

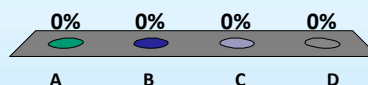


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Which of the following is correct?

- A. The patient has made the situation worse by retaking the medication after experiencing a rash
- B. The Provider should have ordered other tests prior to starting this regimen
- C. Both medications should be discontinued but restarted in two days
- D. A and B are correct



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Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)



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Case 3

- LK is a 45 yo female seen in your clinic diagnosed as HIV positive and tuberculosis.
- Current labs revealed: Electrolytes wnl, serum creatinine 0.7, ALT 23, CBC with differential wnl, HIVRNA 120,000 copies/ml and CD4 325 cells/mm³
- The provider has ordered the following meds: Viramune[®] (Nevirapine) 200mg PO daily x 14 days, then 200mg PO BID thereafter, Truvada[®] (tenofovir/emtricitabine) one tab PO q 24hr

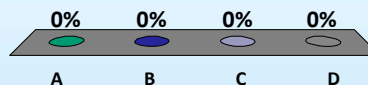


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Which of the following is correct?

- She is at risk for developing hepatotoxicity
- Viramune[®] (Nevirapine) is FDA Pregnancy Category D and should not be used
- Viramune[®] (Nevirapine) will most likely cause serious bone marrow suppression
- All of the above are true



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Factors that Predispose to Hepatotoxicity

- **Concurrent use of hepatotoxins**
 - Drugs: rifampin, INH, etc.
- **HBV or HCV co-infection**
- **Elevated ALT or AST at baseline**
- **Viramune® (Nevirapine) initiation in ARV-naïve patients with Pre-nevirapine CD4 counts > 250 cells/mm³ in women and CD4 counts > 400 cells/mm³ in men**
- **Alcoholism**

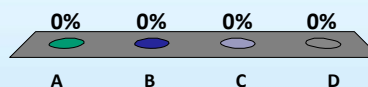


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One month later, this patient develops a severe rash. Which of the following is true?

- A. Viramune® (Nevirapine) can be continued because the rash will resolve within one to two weeks
- B. The patient should stop taking both medications and resume after the rash has cleared
- C. Viramune® (Nevirapine) may cause Stevens-Johnson syndrome and should be discontinued
- D. None of the above are true



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Discussion Points

- **Stevens-Johnson syndrome can occur with Viramune® (Nevirapine) and other NNRTIs within the first few days or weeks of therapy**
- **Also reported with various PIs and NRTIs**
- **Symptoms include:**
 - Skin eruption with mucosal ulcerations
 - Blister formation can occur
 - May develop epidermal detachment and necrosis



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Steven Johnson Syndrome or Toxic Epidermal Necrolysis



<http://www.fromthewilderness.com/images/stevenJohnsonSyndrome2.jpg>

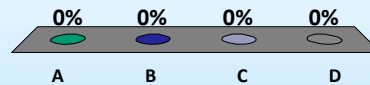


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Which of the following are true regarding Sustiva® (efavirenz)?

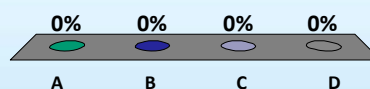
- A. Interference with urine test for cannabinoids and benzodiazepines
- B. May cause severe, vivid dreams
- C. Pregnancy Category D
- D. All of the above are correct



Protease Inhibitors (PIs)

Which of the following is true concerning complications from PIs?

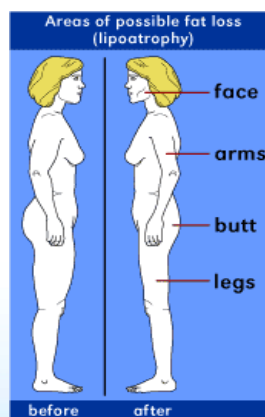
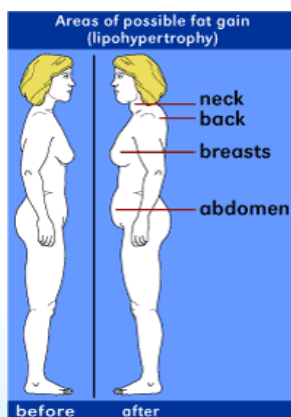
- A. May cause hypoglycemia
- B. All PIs cause significant hyperlipidemia
- C. Are associated with changes in fat distribution in the body
- D. None of the above are true



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Lipodystrophy



http://www.thebody.com/pinf/wise_words/mar05/lipodystrophy.html?m89o



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Lipodystrophy

- Associated ARVs: Lipoatrophy: NRTIs (d4T > ZDV > TDF, ABC, 3TC, FTC), especially when combined with EFV
- Lipohypertrophy: PI- or NNRTI-based regimens and with thymidine analogs (e.g., d4T, ZDV)
- Onset: Gradual (i.e., months after initiation of therapy)
- Symptoms: Lipoatrophy: peripheral fat loss manifested as facial thinning and as thinning of extremities and buttocks (d4T)
- Lipohypertrophy: increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)
- Frequency: High
- Risk Factors: Both lipoatrophy and lipohypertrophy: Low baseline body mass index



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Lipodystrophy

- Prevention (Lipoatrophy): Avoid thymidine analogs (especially when combined with EFV), or switch from ZDV or d4T to ABC or TDF
- Prevention (Lipohypertrophy): Pretreatment diet/exercise program may reduce incidence and extent
- Management: Lipoatrophy: Switch from thymidine analogs to TDF or ABC, which may slow or halt progression but may not fully reverse effects, Injectable poly-L-lactic acid or other injectable fillers for treatment of facial lipoatrophy
- Lipohypertrophy: Liposuction for dorsocervical fat pad enlargement, diet/exercise, Recombinant human growth hormone and GH-releasing hormone analogue under investigation, and Improvement in visceral fat seen in patients on LPV/r switched to ATV/r



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Lipodystrophy Illustrations



“Buffalo hump”



“Facial wasting”



“Crix belly”

<http://www.hivandhepatitis.com/recent/lipo/fataccumulation/1.html#buf>

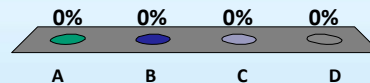


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Which of the following have been reported with PIs?

- A. Prolongation of QT interval
- B. Development of potentially severe cardiac arrhythmias
- C. Hyperglycemia
- D. All of the above



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Cardiac Associated Abnormalities with PIs

- **PIs and cardiovascular complications**
 - Onset within months to years after beginning therapy
 - Myocardial infarction, arrhythmias and stroke has been associated with use
 - Potential mechanisms involve alterations in cardiac conduction and electrophysiology

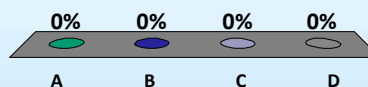


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A DEXA scan may be important for which of the following situations?

- A. Patients receiving Kaletra[®] 200/50mg (lopinavir/ritonavir) combination
- B. Patients receiving Sustiva[®] (efavirenz)
- C. All patients receiving Epivir[®] (lamivudine)
- D. A and B only



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Osteopenia/Osteoporosis

- Osteopenia (defined as DEXA scan t-score of 1–2.5 SD from normal) or osteoporosis (t-score >2.5 SD from normal)
- Associated ARVs: Some evidence for bone loss after starting variety of ARVs; association with TDF or d4T; similar rate of bone loss with EFV- (-2.3%) or LPV/r- (-2.5%) based regimens over 96-week period.
- Onset: Months to years after starting ART
- Symptoms: Generally asymptomatic, bone pain, increased risk of fractures



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Osteopenia/Osteoporosis

- **Risk factors (General):**
 - Low body weight, history of significant weight loss,
 - Female, White, Southeast Asian, older age,
 - Alcohol use, smoking, caffeine,
 - Hypogonadism, hyperthyroidism, corticosteroids, and Vit D deficiency
- **Risk Factors (HIV):**
 - Low CD4 count, duration of HIV, lipoatrophy, increased lactic acid levels, and TDF exposure
- **Frequency:** Wide range depending on methodology and patient population; rate appears much higher than seen in the general population: 20-54% for osteopenia and 2-27% for osteoporosis.



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Osteopenia/Osteoporosis

- Prevention:
 - **Consider assessment of bone mineral density with DEXA scan Weight-bearing exercise, Calcium and vitamin D supplementation, and Hormone replacement**
- Management:
 - **Switch from potentially contributing ARVs (i.e., d4T or TDF), increase exercise, improve diet, decrease alcohol and tobacco use, increase calcium and vitamin D supplementation, bisphosphonate (e.g., once- weekly alendronate), hormone replacement, and intranasal calcitonin**



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Other Major Adverse Effects

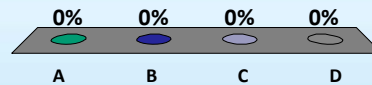


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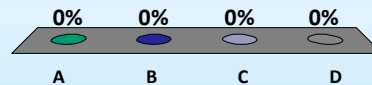
A patient experiences numbness and paresthesia in feet, which of the following is a most likely cause?

- A. Videx EC[®] (didanosine)**
- B. Zerit[®] (stavudine)**
- C. Fuzeon[®] (enfuvirtide)**
- D. A and B**



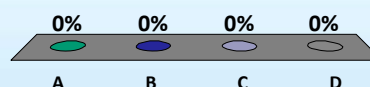
Which of the following drugs should be considered to treat peripheral neuropathy?

- A. Neurontin[®] (gabapentin)**
- B. Motrin[®] (ibuprofen)**
- C. Dilantin[®] (phenytoin)**
- D. All of the above**



Which ARVs are associated with bleeding events?

- A. Intelence® (etravirine)
- B. Aptivus® (tipranivir/ritonavir)
- C. Epivir® (lamivudine)
- D. None of the above



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Discussion Points

- Associated ARVs: TPV/r
- Frequency: For ICH: 24 reported cases with TPV/r use, including 12 fatalities.
- Median time to ICH event: 525 days on TPV/r therapy.
- Risk Factors:
 - **CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, receiving anticoagulant or anti-platelet agents including vitamin E;**
- Prevention:
 - **Avoid vitamin E supplements, particularly with the oral solution formulation of TPV; Avoid using TPV/r in patients at risk of ICH**



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Role of the Clinician in Understanding Complications

- **Understanding the complications of antiretroviral therapy is critically important because:**
 - A clear understanding can prevent problems that can cause significant morbidity
 - Understanding adverse effects can improve patient adherence to therapy
- **Staying abreast to latest changes is imperative as new information continues to emerge!**



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References

- **Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. December 1, 2009. Department of Health and Human Services**
- http://www.thebody.com/pinf/wise_words/mar05/lipodystrophy.html?m89o
- <http://www.hivandhepatitis.com/recent/lipo/fataccumulation/1.html#buf>



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