



20th ANNUAL HIV CONFERENCE
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May 13-14, 2011
Orlando, FL

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Liver, Kidney, Bone: Emerging Issues of Long Term Antiretroviral Therapy

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Lecture Objectives

Upon completion of this lecture the participant should be able to:

- Discuss the specific long term effects of antiretroviral use on the liver, kidney and bone
- Discuss signs and symptoms of toxicity and recommend alternatives
- Identify patient education needs for healthful lifestyle behaviors that will delay adverse effects



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Drug Induced Liver Injury

- **General Facts**
 - Incidence between 1 in 1000 to 1 in 100,000 depending on reports cited
 - Believed to be underreported
 - Drugs that are hepatotoxic may exhibit characteristic clinical findings that include:
 - Abnormal liver function tests
 - Latency of symptom onset
 - Presence of absence of immune hypersensitivity
 - Course of reaction after drug withdrawal



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Drug Induced Liver Injury

- **Definition:**
 - Drug induced liver injury is defined as the elevation of liver enzyme and/or bilirubin levels in association with the use of a medication
 - The term "hepatotoxicity" may be misleading because the injury may not be due to a toxic drug as other co-morbidities may be contributing factors (e.g. acute viral hepatitis, reactivation of chronic hepatitis B or C, alcohol ingestion)



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Significance of Laboratory Diagnosis

- **An elevation of transaminase levels (AST, ALT) is a sensitive signal for liver injury but it may not be specific or clinically relevant because many times values improve despite continuation of therapy**
- **In the majority of cases, enzyme elevations are not accompanied by symptoms**



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Significance of Laboratory Diagnosis

- A bilirubin elevation due to drug induced liver injury is a more ominous finding whereas 10% of patients with jaundice die or need a liver transplant (the so-called Zimmerman's rule)

Severe Drug Induced Injury: World Health Organization

- World Health Organization defines severe drug induced liver injury as:
 - Elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels greater than 5 times (grade 3) or greater than 10 times (grade 4) the upper limit of normal for the laboratory
 - In patients with elevated baseline enzyme levels, an elevation of 3.5 to 5.0 times the upper limit of normal is severe

Patients Susceptible to Drug Induced Liver Injury

- **Patients with chronic viral illness, such as HIV or HCV are more prone to develop hepatotoxicity caused by HAART and antituberculosis medications**
 - HCV is associated with a 2-10 fold chance of developing elevated transminases during HAART compared with those who do not
 - Between 7% to 13% of coinfectd HIV infected patients develop grade 3 or 4



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Patients Susceptible to Drug Induced Liver Injury

- **Other risk factors for increased injury include:**
 - Alcohol use
 - HBV co-infection
- **Injury involving Protease Inhibitors and NNRTIs is generally noted within 18 to 20 weeks of initiating therapy**



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Drug Induced Liver Injury

- Drug induced injury accounts for more than 50% of acute liver failure cases with acetaminophen being the most common
- Accounts for about 10% of liver transplants according to recent reports

Characteristics of Drug Induced Hepatotoxicity

- Two major mechanisms of toxicity include:
 - Direct drug induced injury
 - These reactions are usually dose dependent
 - Reproducible and has a predictable course
 - Time course between initiation of the drug and hepatotoxicity is usually consistent from patient to patient
 - The dosage to produce toxicity is generally consistent from person to person
 - Can present as hepatocellular, cholestatic or mixed
 - Can occur as result of biotransformation (eg acetaminophen)

Characteristics of Drug Induced Hepatotoxicity

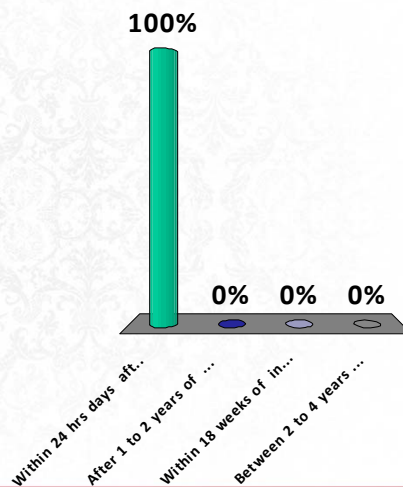
- Idiosyncratic drug induced injury
(unpredictable)
 - Manifested as a delay or latency period from anywhere from 5 to 90 days after drug ingestion
 - Classified as hepatocellular, cholestatic or mixed
 - Divided into two main categories:
 - Metabolic
 - Immunological

Characteristics of Drug Induced Injury

- **Metabolic Drug-Induced Injury**
 - Metabolic reactions can occur from a specific genetic polymorphism resulting in the formation of a toxic metabolite. The reaction may not be reproducible from person to person
- **Immunologic reactions**
 - Hypersensitivity to the drug. Accompanying features include mild fever, eosinophilia, atypical lymphocytosis, Stevens-Johnson Syndrome and toxic epidermal necrolysis
 - Can be reproduced via re-challenge...not advisable

Hepatotoxicity from NNRTIs (Nevirapine) Usually Occur

1. Within 24 hrs days after initiating therapy
2. After 1 to 2 years of therapy
3. Within 18 weeks of initiating therapy
4. Between 2 to 4 years after therapy



Hepatotoxic Drugs Used in HIV Drug Therapy Management

- Antiretrovirals
- Antihyperlipidemics
- Antibiotics
- Others
 - Herbal Preparations
 - Oral Hypoglycemics
 - Psychotropics

ANTIRETROVIRALS



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ART Options


- NRTIs (Nucleoside OR Nucleotide Reverse Transcriptase Inhibitors, aka “Nukes”)
- NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors, aka “Non-Nukes”)
- PIs (Protease Inhibitors)
- Fusion Inhibitors
- Entry Inhibitors
- Integrase Inhibitors



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Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI's)	
Agent	Approved
<ul style="list-style-type: none"> • Zidovudine (AZT, ZDV, Retrovir®) • Didanosine (ddl, Videx®, Videx EC®) 10/91 • Zalcitabine (ddC, Hivid®) • Stavudine (d4T, Zerit®) • Lamivudine (3TC, Epivir®) 11/95 • Abacavir (ABC, Ziagen®) • Combivir® (AZT/3TC) • Trizivir® (AZT/3TC/ABC) • Tenofovir (TDF, Viread®)* • Emtricitabine (FTC, Emtriva®) • Epzicom® (ABC/3TC) • Truvada® (FTC/TDF) 	<p>3/87</p> <p>6/92</p> <p>6/94</p> <p>12/98</p> <p>9/97</p> <p>11/00</p> <p>10/01</p> <p>7/03</p> <p>8/04</p> <p>8/04</p>




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Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's)	
Agent	Approved
<ul style="list-style-type: none"> • Nevirapine (NVP, Viramune®) • Delavirdine (DLV, Rescriptor®) • Efavirenz (EFV, Sustiva®) 9/98 • Etravirine (Intelence®) 	<p>6/96</p> <p>4/97</p> <p>1/2008</p>




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Protease Inhibitors (PI's)	
Agent	Approved
• Saquinavir-HGC (SQV-HGC, Invirase®)	12/95
• Ritonavir (RTV, Norvir®)	3/96
• Indinavir (IDV, Crixivan®)	3/96
• Nelfinavir (NFV, Viracept®) 3/97	
• Saquinavir-SGC (SQV-SGC, Fortovase®)	11/97
• Amprenavir (APV, Agenerase®)	4/99
• Lopinavir/ritonavir (KAL, Kaletra®)	9/00
• Atazanavir (ATV, Reyataz®)	6/03
• Fosamprenavir (fos-APV, Lexiva®)	10/03
• Tipranavir (TPV, Aptivus®)	6/05
• Darunavir (DRV, Prezista®)	6/06



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Fusion and Entry Inhibitors	
Agent	Approved Fusion
• Enfuvirtide (T-20, Fuzeon®)	3/03
Entry Inhibitor (CCR5 Inhibitor)	
• Maraviroc (Selzentry®)	8/07



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Integrase Inhibitor

➤ Raltegravir (Isentress)

- Introduced October 2007
- New class used in treatment experienced patients
- Used in patients with multiply-resistance strains of HIV
- Inhibition of integrase prevents insertion of HIV DNA into the human DNA genome, thus blocking the ability of HIV to replicate



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Liver Damage with ARVs

- **Hepatotoxicity due to HAART is common with up to 30% of patients on HAART experiencing World Health Organization grade 3 liver enzyme elevations**



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ALL Antiretrovirals Cause Hepatic Injury

- Protease Inhibitors cause hepatotoxicity at ANY time during therapy
- Nevirapine usually causes damage within first 18 weeks
- NRTIs
 - Mitochondrial toxicity is associated with NRTIs (e.g. stavudine, didanosine) and long term monitoring is required (more than 1 year) for development of hepatotoxicity
 - Hepatic steatosis and lactic acidosis
- Maraviroc
- Raltegravir is less



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Evaluation of Hepatotoxicity

- Evaluate AST, ALT, bilirubin
- Mechanism of toxicity
- Clinical features
 - NRTIs (stavudine, didanosine)
 - NNRTIs
 - Pis
 - Maraviroc

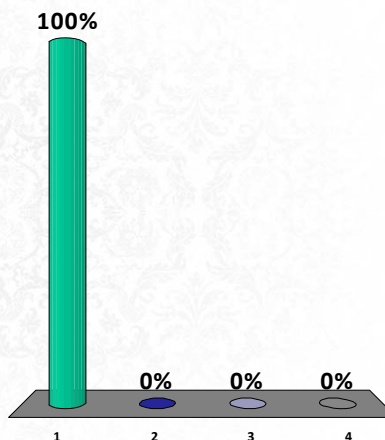


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Protease Inhibitors can cause hepatic damage:

1. Most often within the first few days of therapy
2. After 14 days of therapy
3. At any time during therapy
4. Only after 2 to 3 years



Effects of ARV Therapy on the Kidney

Other Causes of Renal Disease in HIV Infection

- **Acute kidney injury** occurs frequently in HIV infection
 - The incidence of acute kidney injury has been reported to be a cause of complications of 6% of hospital stays in among HIV patients
- **Chronic Kidney Disease (CKD)** is common in HIV with prevalence rates up to 4 times that of the general population



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Other Causes of Renal Disease in HIV Infection

- **Independent risk factors associated with CKD in people with HIV include:**
 - Older age
 - History of previous opportunistic illness
 - Presence of relevant medical comorbidities such as diabetes and hypertension



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Other Causes of Renal Disease in HIV Infection

- In most urban North American surveys, African American race is a predominant risk factor for CKD in part related to a racial predisposition to HIV-associated nephropathy (HIVAN)
- HIVAN commonly occurs with advanced HIV and typically improves with treatment of HIV



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Effects of ARV Therapy on Renal Function

- The proportion of CKD in HIV patients attributable to ARV use is relatively low
- Initiation of ARV therapy is generally associated with improvements in renal function especially in patients with low CD4 counts and high viral loads at time of ARV initiation and in those with preexisting kidney disease



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Effects of ARV Therapy on Renal Function

- With increasing availability of ARV, the risk of ESRD has decreased by more than 50% in some populations studied
- Survival of HIV-infected persons with ESRD is prolonged. This has led to increasing prevalence of CKD in HIV populations



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Nephrotoxicity and ARV Therapy

- Despite the benefits of ARV use in HIV infection, these agents can be nephrotoxic
- There are case reports with almost every ARV but there are three agents with well-established associations with direct nephrotoxicity supported by numerous case reports and large cohort studies: indinavir, atazanavir and tenofovir



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Indinavir Nephrotoxicity

- **Indinavir-associated nephrotoxicity:
Common side effect but obsolete drug**
- **Very common in 1996 but due to concerns of inconvenient dosing, meal restrictions and nephrolithiasis and newer PIs, it has been replaced and is very seldom prescribed**



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Indinavir Nephrotoxicity

- **Indinavir is notorious for causing renal and urologic toxicity mediated by tubular crystallization (15% excreted unchanged in urine)**
- **Asymptomatic indinavir crystalluria is very common and occurs in two-thirds of treated patients**
- **Risk Factors**
 - Dehydration, increased serum levels, concurrent acyclovir, trimethoprim-sulfa use



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Different Presentations of Indinavir Nephrotoxicity

- Approximately 4% will experience acute urolithiasis due to crystalluria, sometimes complicated by obstructive uropathy and acute renal failure
- Flank pain and dysuria in the absence of frank urolithiasis. It is thought that crystal sludging results in tubular obstruction, with distention and/or bladder wall irritation
- Sub-acute or chronic tubulointerstitial nephritis



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Recommendations to Minimize Effects

- Drink at least 1.5 liters of water daily
- Periodic urinalysis for pyuria and monitoring of serum creatinine
- Switching to a more efficacious alternative antiretroviral agent is the best strategy!



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Atazanavir-Associated Nephrotoxicity

- Atazanavir is a widely used agent but nephrotoxicity is not a major side effect
- Up to 8% is excreted unchanged via the kidney and it is poorly soluble in urine and will precipitate at alkaline pH
- In contrast to indinavir, renal toxicity, crytalluria or nephrolithiasis was not observed in initial trials with this ARV



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Atazanavir Nephrotoxicity

- Postmarketing review has revealed documented cases of nephrolithiasis through the FDA adverse reporting system
- A retrospective study in France found 11 confirmed cases of nephrolithiasis among 1,134 patients (frequency about 0.97%)



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Atazanvir Nephrotoxicity

- **Although the possibility of nephrolithiasis exists, specific preventive or monitoring strategies are not routinely recommended**
- **In some cases, atazanavir was safely reintroduced with instruction to drink ample acidic pH fluids. Recurrence rates are low**



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Tenofovir Nephrotoxicity

- **An increasingly recognized rare adverse event for a commonly used ARV agent**
- **Although well tolerated with few toxicities during clinical trials, multiple case reports have linked tenofovir with:**
 - Proximal renal tubulopathy
 - Urinary phosphate wasting
 - Decreased bone mineral density
 - Impaired glomerular filtration



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Tenofovir Nephrotoxicity

- Reported cases suggest that renal damage manifests as proximal tubular injury with associated reduction in glomerular filtration
- Patients often develop glycosuria, tubular proteinuria, low serum phosphate and increased serum creatinine
- Some patients develop Fanconi's syndrome and/or reduced bone mineral density



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Tenofovir Nephrotoxicity

- Rarely is dialysis required
- Rarely is symptomatic fracture experienced



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Risk Factors for Tenofovir Nephrotoxicity

- Risk factors are not well established
- Observational studies have suggested the importance of:
 - Comorbid renal dysfunction
 - Advanced age
 - Co-administration of didanosine
 - An association between tenofovir related nephrotoxicity and protease inhibitor use has been suggested but is not conclusive

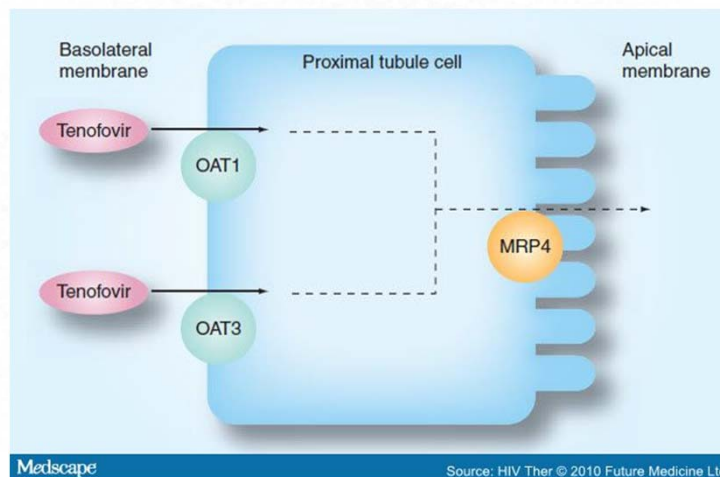


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Mechanism of Tenofovir-Related Nephrotoxicity



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Mechanisms Involved in Tenofovir Nephrotoxicity

- Tenofovir is renally excreted via a combination of glomerular filtration and active tubular secretion
- In vitro studies suggest that TDF is toxic to mitochondrial function in proximal convoluted tubule cells at high concentrations
- Disruption of mitochondrial function compromises tubular cell integrity and leads to tubule necrosis, Fanconi syndrome and decreased GFR



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Tenofovir Nephrotoxicity

- Intracellular accumulation of TDF may be influenced by multidrug resistance-associated protein transporter (MRP) which is competitively inhibited by protease inhibitors (see diagram)
- Didanosine coadministration with DF may also lead to additional or synergistic mitochondrial toxicity in the proximal tubule cell



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Prevention of TDF Nephrotoxicity

- Ensure appropriate dose reduction in patients with preexisting renal dysfunction, especially when GFR falls below 50 ml/min
- Ensure that comorbid renal disease is managed and that other nephrotoxic drugs are avoided



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Monitoring for Nephrotoxicity with TDF

- Recommendations for regular laboratory monitoring vary
- Most authorities suggest semi-annually
 - Measurement of renal function (can use Cockcroft-Gault Method),
 - Serum phosphorous
 - Urinalysis for protein and glucose
- Elevated fractional urinary excretion of phosphate is an early marker of tubular dysfunction and might be useful



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Monitoring for TDF Nephrotoxicity

- **Some investigators suggest monitoring only those patients presumed to be at increased risk**
 - i.e. preexisting renal dysfunction who are either also taking other potentially nephrotoxic agents or who have relevant medical comorbidities such as diabetes or hypertension
- **Other investigators recommend regular monitoring of all patients**



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Summary with Kidney Effects of ARV Therapy

- **Although there have been reports with virtually every ARV as causing renal dysfunction, many have been unsubstantiated**
- **Of the three agents where reports have been identified, tenofovir is the most common and monitoring for its prevention must be included in the monitoring plan for these patients**



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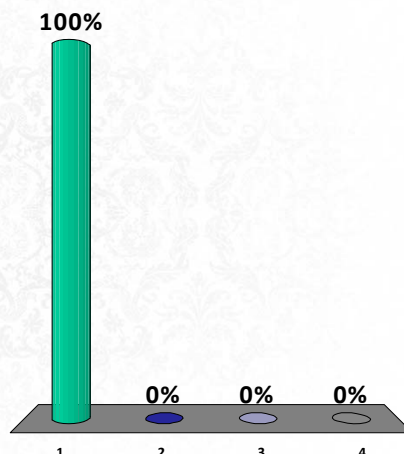
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Tenofovir induced nephrotoxicity can cause?

1. Potassium wasting
2. Sodium wasting
3. Hyperphosphatemia
4. **None of the above**



Effects of ARV Management on Bone

- Low bone mineral density (BMD) is prevalent in the HIV population as this population becomes older due to the success of ARV therapy
- Causes of low BMD are multifactorial and include interactions between HIV infection, traditional osteoporosis risk factors and the effect of ARV therapy

Bone Disease and ARVs

- **Classification of BMD:**
 - Normal
 - Osteopenia
 - Osteoporosis
- **Classification depends upon the number of standard deviations (SD) below the mean BMD for a healthy young (25-35 years old), properly sexed and ethnicity matched (T score)**



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Bone Disease and ARVs

- **In older populations the risk of bone fracture almost doubles for each SD below the young normal mean**
- **In younger patients, a Z score is used to determine bone density**
- **Bone density can be worse in patients receiving ARV therapy (particularly NRTIs such as tenofovir), in advanced HIV and pubertal males**



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Classifications and Definitions

- **Osteoporosis**
 - Definition
 - BMD measured by dual-energy x-ray absorptiometry (DXA)
 - A T score less than or equal to -2.5 at the hip or spine defines osteoporosis in men 50 years old and older and in post-menopausal women
 - For those under 50 years old, a Z-score with a value less than -2.0 is regarded as abnormal

Classification continued

- **Osteopenia**
 - Definition
 - Patients with a T score between -1 and -2.49 are considered to have osteopenia
- **Osteomalacia**
 - Occurs when mineralization of the bone matrix is impaired, usually caused by deficiency of Vitamin D. Decreased BMD and fractures may occur

Low BMD in HIV-Infected Patients

- Studies have demonstrated low BMD in both younger and older HIV-infected patients
- BMD decreases by 2 to 6% in HIV-infected patients within first 2 years after initiation of various ARV regimens.



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Low BMD in HIV Infected Patients

- Recent studies have reported that fracture rates are higher in HIV patients when compared to controls
- The presence of osteopenia in naïve patients suggest that viremia can impact BMD. Systemic inflammation effects on bone remodeling may be the cause



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Possible Etiologies of low BMD in HIV Infection

- HIV infection
- Low vitamin D levels
- Use of Tenofovir
 - No recommendations against use
- Tobacco and alcohol use
- Lipoatrophy

Screening for Bone Disease

- DXA is recommended in the following situations:
 - Individuals of any age with a fragility fracture
 - Women 65 years old and older
 - Men 70 years old and older

Screening for Bone Disease in HIV

- **HIV-infected post-menopausal women and men 50 years of age and older should have DXA**
 - Repeat DXA every 2 years
 - Infectious Diseases Society of American Primary Care Guidelines recommend DXA for HIV patients over 50 if they have an additional risk factor for osteopenia/osteoporosis



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Other Causes of Osteoporosis

- **In HIV-infected patients, low BMD has been associated with:**
 - Low body weight
 - Decreased testosterone
 - Decreased estrogen
 - Malabsorption
 - Smoking
 - Substance abuse (alcohol and opiates)
 - Low CD4,
 - Insulin resistance



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When Should Treatment Be Implemented?

- **Post-menopausal women and men 50 years and older with a T-score of the total hip, femoral neck or lumbar spine less than -2.5 or in persons with a history of fragility fracture**
- **Persons with osteopenia with a WHO Fracture Assessment Tool (FRAX) risk more than or equal to 20%**



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Treatment for Low BMD

- **Identify and correct Vitamin D deficiency and phosphorous levels**
 - Calcium
 - Phosphorous
- **Use of biphosphates**
 - Commonly used agents
 - Alendronate (Fosamax®)
 - Ibandronate (Boniva®)
 - Zoledronic acid (Reclast®)



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General Advice for Bone Health

- 1000 to 1500 mg of elemental calcium daily (note varying elemental contents)
- 800 to 1000 IU of Vitamin D
- Muscle strengthening and balancing exercises
- 30 minutes of weight bearing exercise for women at least 3 times weekly
- Stop smoking and limit alcohol to 3 times weekly



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Summary

- Advances in antiretroviral therapy have resulted in prolonged life
- HIV-infected patients experience the same co-morbidities as non infected patients
- Monitoring long term effects of the infection and the effects of ARV meds is important for overall success!!



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