Management of Antiretroviral Therapy Complications

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- HAART has changed the landscape of HIV disease from an almost uniformly fatal disease to a chronic manageable one.
- Unfortunately, up to 25% of all patients discontinue their initial HAART regimen because of treatment failure, toxic effects or noncompliance within the first eight months of therapy
- **Prompt understanding and management of adverse effects becomes very important for good adherence, which can lead to decreased drug resistance**

Available Antiretroviral Agents

1. Nucleos(t)ide RTIs

- Zidovudine (ZDV)
- Didanosine (ddI)
- ~~Zalcitabine (ddC)~~
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Tenofovir DF (TDF)

Approved 1992 and withdrawn 2006

- it caused oral and esophageal ulcers
- dose-related morbilliform exanthems,
- occasional hypersensitivity syndromes

2. Non-nucleoside RTIs

- Nevirapine (NVP)
- Efavirenz (EFV)
- Etravirine (ETR)
- Rilpivirine (RPV)
- Delavirdine (DLV)

3. Protease Inhibitors

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- ~~Amprenavir (APV)~~ *discontinued 2004*
- Lopinavir/r (LPV/r)
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Darunavir (DRV)

4. Integrase Inhibitors

- Raltegravir (RAL)
- Dolutegravir (DTG)
- Elvitegravir (EVG)

5. Fusion Inhibitor

- Enfuvirtide (T-20)

6. CCR5 Antagonist

- Maraviroc (MVC)

Boosters

- Ritonavir (RTV)
- Cobicistat* (COBI)

Therapeutic Goals of ART

- **Efficacy:**
  - optimal and durable efficacy to maintain viral suppression and improve immune function
- **Safely:**
  - **favorable tolerability and toxicities**
    - Patient's underlying conditions
      - Liver , kidney and bone marrow function
    - Concomitant medication
      - Drug-drug interaction
    - Prior history of drug intolerance

When you think about ART complications?

- When to start antiretroviral therapy?
  - Choose the best regimens of ARV
  - Aware for drug-drug interaction
  - Counselling patients about complications from ART

“The best regimen is the one the patient will take”

When you think about ART complications?

- When you want to start antiretroviral therapy?
  - Choose the best regimens of ARV
  - Aware for drug-drug interaction
  - Counselling patients about complications from ART
- **When patients got complication after start antiretroviral therapy ?**

HIV patients with complications

- HIV infection
- New opportunistic infection (IRIS)
- Adverse effects from medication (ART or prophylaxis OIs)

Complications of Antiretroviral Therapy

1. **Adverse effects of Antiretroviral therapy (ART)**
   - Severity: life-threatening adverse effects , serious adverse effects
   - Duration: short term adverse effects, long term adverse effects
2. **Drug-drug interaction**
   - Serious : ergotism (EFV, RTV) , Torsades de Pointes (PIs), rhabdomyolysis (statin), symptomatic hypotension, Excessive sedative, Cushing's syndrome
3. **Immune reconstitution inflammatory syndrome (IRIS)**
   - Most often in patients who have rapid response to therapy
   - Usually, treatment with ARV should continue through IRIS

Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study

*Jacques Fellay, Karim Boubaker, Bruno Ledergerber, Enos Bernasconi, Hansjakob Furrer, Manuel Battegay, Bernard Hirschel, Pietro Vernazza, Patrick Francioli, Gilbert Greub, Markus Flepp, Amalio Telenti, for the Swiss HIV Cohort Study**

- Assessed prevalence of adverse events in 1,160 patients who were receiving ART.
- Reported ADRs in 74% of their cases
  - 47% (545 of 1,160) of patients presented with clinical and 27% (194 of 712) with laboratory adverse events

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Immune reconstitution inflammatory syndrome (IRIS) after ART

IRIS	Present study (*n* = 90)
Herpes zoster	11 (12.2%)
Herpes simplex	05 (5.6%)
Tuberculosis	04 (4.4%)
Human papilloma virus infection	00
Molluscum contagiosum	00
Total	20 (22.2%)

Adverse effects of antiretroviral treatment. Indian J Dermatol Venereol Leprol 2008;74:234-7

Classification of ART adverse effects

1. **Short term adverse effects**
   - **Life-threatening adverse effects**
     - Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hepatic necrosis, hypersensitivity reaction or severe mitochondrial toxicity (lactic acidosis, hepatic steatosis ± pancreatitis)
   - **Serious adverse effects**
     - Skin rash, bone marrow suppression, hepatitis, nephrotoxicity or renal stone
2. **Long term adverse effects**
   - Lipodystrophy, insulin resistance, dyslipidemia, cardiovascular system or osteopenia/osteoporosis

Classification of ART adverse effects

- Class Specific Toxicities

NRTIs	Mitochondrial DNA toxicity
N(t)RTI	Proximal renal tubular dysfunction
NNRTIs	Rash, Hypersensitivity reactions
PIs	Nausea, diarrhea, rash, dyslipidemia and insulin resistance

- Drug Specific Toxicities
- Syndrome or Organ Specific Toxicities

The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient.

Risk factors for ART adverse effects

- **Gender:** women (CD4 cell count > 250 cells/mm^3) have a higher risk to develop SJS, rashes and hepatotoxicity from NVP.
- Concomitant use of medications with overlapping and additive toxicities
- Drug-drug interactions
- **Genetic factors:** ABC →hypersensitivity reaction
- Comorbid conditions: alcoholism, chronic viral hepatitis co-infection

Adverse effects associated with Drug and Classes Specific Toxicities

Antiretroviral drugs	Adverse Events
1. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	
Abacavir (ABC)	**Hypersensitivity reaction (HSR)**
Didanosine (ddI)	- pancreatitis, peripheral neuropathy - Nausea, diarrhea - Retina change, optic neuritis - Noncirrhotic portal hypertension
Lamivudine (3TC)	- headache, dry mouth - In patients with HIV-HBV coinfection, hepatits may flare upon discontinuation of 3TC
Emtricitabine (FTC)	- headache, nausea, insomnia - Hyperpigmentation of palms and soles (most frequently in dark-skinned people) - In patients with HIV-HBV coinfection, hepatits may flare upon discontinuation of FTC

Antiretroviral drugs	Adverse Events
1. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	
Stavudine (d4T)	- pancreatitis, lactic acidosis and hepatic steatosis, peripheral neuropathy (esp. combined with ddI) - **Lipodystrophy** - Dyslipidemia, insulin resistance
Tenofovir disoproxil fumarate (TDF)	- **Proximal tubulopathy, Fanconi syndrome** - Acute or chronic renal insufficiency - **Decrease bone mineral density** - Osteomalacia - Headache, diarrhea, nausea, vomiting, asthenia - In patients with HIV-HBV coinfection, hepatits may flare upon discontinuation of TDF
Zidovudine (AZT, ZDV)	- **Bone marrow suppression: macrocytic anemia, neutropenia** - Nausea, vomiting, headache, fatigue - **Myalgia, myopathy** - **Hyperpigmentation of skin and nails**

Antiretroviral drugs	Adverse Events
2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Efavirenz (EFV)	- **CNS** : headache, dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, depression, psychosis and suicidal ideation - Rash: MP rash , rare SJS - **Lipodystrophy, gynecomastia**
Etravirine (ETV)	- rash, HSR - Nausea, vomiting, abdominal pain - Hypertension, peripheral neuropathy - Dyslipidemia (increased cholesterol and triglyceride)
Nevirapine (NVP)	- Rash : SJS and TEN - Hepatitis→ fatal hepatic necrosis, liver failure
Rilpivirine (RPV)	- CNS: less than EFV; dizziness, abnormal dream, insomnia, depression - QT prolongation if using dose > 25 mg - dyslipidemia
Delavirdine (DLV)	- Nausea, diarrhea, fatigue, hepatitis

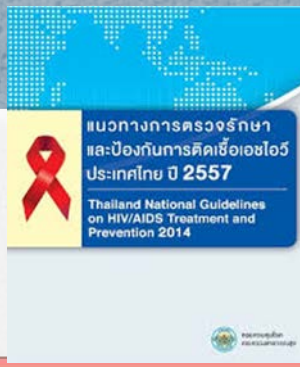
Antiretroviral drugs	Adverse Events
3. Protease Inhibitors (PIs)	
Atazanavir (ATV)	- Asymptomatic indirect hyperbilirubinemia (with or without jaundice, but without increased hepatic transaminase) - Rash (20% can continue treatment) - PR prolongation , cholelithiasis, nephrolithiasis
Darunavir (DRV)	- Rash (10% severe reaction)(structure similar to sulfonamide)
Indinavir (IDV)	- Indirect hyperbilirubinemia, cholelithiasis - Nephrolithiasis, Flank pain, renal insufficiency - Alopecia, dry skin and mucous membranes, paronychia, ingrown toe nails
Lopinavir/ritonavir (LPV/r)	- GI intolerance: nausea, vomiting, diarrhea - Hepatitis - Dyslipidemia (hypertriglyceride), lipodystrophy, insulin resistance - Increased bleeding episodes in patient with haemophilia - PR and QT prolongation

Antiretroviral drugs	Adverse Events
3. Protease Inhibitors (PIs)	
Ritonavir (RTV)	- GI intolerance: nausea, vomiting, diarrhea - Paresthesia, taste perversion, circumoral numbness - Dyslipidemia (hypertriglyceride), lipodystrophy, insulin resistance - Increased bleeding episodes in patient with haemophilia - hyperuricemia
Saquinavir (SQV)	- Rash - Prolong QT interval - Oral ulcer - Hyperprolactinemia (rare)
Tipranavir (TPV)	- Hepatotoxicity - Intracranial hemorrhage associated with CNS lesions, prior trauma, HT, alcohol abuse , coagulopathy and received anti-coagulant , anti-platelet and vitamin - ระวังการใช้ในผู้ที่แพ้ยา sulfonamide

Antiretroviral drugs	Adverse Events
4. Integrase Strand Transfer Inhibitor (INSTIs)	
Raltegravir (RAL)	- Rash : prusitus, MP rash, SJS/TEN - Headache, insomnia, dizziness, fatigue - Nausea, vomiting, diarrhea - **Increased creatine kinase level , myopathy, myositis or rhabdomyolysis**
Elvitegravir (EVG)/COBI	- Nausea, vomiting, diarrhea - Upper respiratory tract infections - Renal insufficiency : decreased tubular secretion of creatinine but no effect to glomerular function (increased serum creatinine 0.4 mg/dL)
Dolutegravir (DTG)	- HSR < 1% - Headache , insomnia - Myositis - Hepatitis (esp. HBV or HCV coinfection) - Renal insufficiency : decreased tubular secretion of creatinine but no effect to glomerular function (increased serum creatinine 0.11 mg/dL in first 4 weeks)

Antiretroviral drugs	Adverse Events
5. Entry Inhibitor (EI)	
Maraviroc (MRV)	- Fever, cough and upper respiratory tract infection - Rash - Nausea, diarrhea, hepatitis and abdominal pain - Postural hypotension Joint pain, muscle pain
6. Fusion Inhibitor (FI)	
Enfuvirtide (T20)	- Injection site reactions: erythema, cysts, and nodules - Eosiophilic hypersensitivity reaction (<1%) - Neutropenia - Possible increased frequency of bacterial pneumonia
Pharmacokinetic Enhancers	
Cobicistat	- Increased serum creatinine, proteinuria - Nausea, diarrhea

การตรวจทางห้องปฏิบัติการ	เมื่อทราบว่าติดเชื้อครั้งแรก	ในปีแรก	ในปีต่อ ๆ ไป	หมาย
ระดับ CD4	✓	ที่ 6 และ 12 เดือน	- ที่ 6 และ 12 เดือนจนกว่า CD4 > 350 cells/mm^3 และ VL < 50 copies/mL ให้ตรวจปีละ 1 ครั้ง	
ปริมาณไวรัส (VL)		ที่ 3 และ 6 เดือน หลังเริ่มยา	ถ้า VL < 50 copies/mL ให้ตรวจปีละ 1 ครั้งถ้า VL ≥ 50 copies/mL ให้พิจารณาเรื่องการดื้อยาและปฏิบัติตามแนวทางการดื้อยา	• ควรตรวจทุกครั้ง ก่อนที่จะมีการปรับเปลี่ สูตรยาอันเนื่องมาจากผลข้างเคียงของยา
HBsAg	✓			ตรวจซ้ำถ้ามีความเสี่ยง
Anti-HCV	✓		เมื่อมีข้อบ่งชี้ในกลุ่มเสี่ยง	กลุ่มเสี่ยง: IDU ประวัติเคยต้องขังในเรือน มาก่อน MSM คู่ของผู้ป่วยไวรัสตับอักเสบซี รอยสัก ประวัติเคยได้รับเลือดมาก่อน
Syphilis (VDRL)	✓		เมื่อมีข้อบ่งชี้	บางกลุ่มควรคัดกรองซ้ำ เช่น MSM ทุก 6 เดื SW ทุก 3 เดือน
ALT	✓	เมื่อมีข้อบ่งชี้	เมื่อมีข้อบ่งชี้	ควรตรวจซ้ำที่ 3 เดือนแรกของการให้ยาถ้ ไวรัสตับอักเสบร่วมด้วยหรือดื่มสุราหรือมี ข้างเคียงของยา



การตรวจทางห้องปฏิบัติการ	เมื่อทราบว่าติดเชื้อครั้งแรก	ในปีแรก	ในปีต่อ ๆ ไป	หมายเหตุ
Creatinine	✓	ที่ 6 และ 12 เดือน	ปีละ 1 ครั้ง หรือเมื่อมีข้อบ่งชี้	• ถ้ามีโรคประจำตัว เช่น เบาหวาน ความดันโลหิตสูง อายุมากกว่า 50 ปี น้ำหนักตัวน้อยกว่า 50 kg หรือเคยได้ IDV ควรตรวจทุก 6 เดือน • ในทุกรายที่ได้ TDF หรือกำลังได้ IDV ควรตรวจทุก 6 เดือน
Total cholesterol Triglyceride	กรณีกลุ่มเสี่ยงหรือมีโรคประจำตัว	ปีละ 1 ครั้ง หรือเมื่อมีข้อบ่งชี้	ปีละ 1 ครั้ง หรือเมื่อมีข้อบ่งชี้	• อายุ < 35 ปี และไม่มีโรคประจำตัว ตรวจได้ไม่เกิน 1 ครั้ง/ปี • อายุ < 35 ปี และมีโรคประจำตัว ตรวจได้ไม่เกิน 2 ครั้ง/ปี • อายุ 35 ปีขึ้นไป ตรวจได้ไม่เกิน 2 ครั้ง/ปี
Fasting blood sugar	กรณีกลุ่มเสี่ยงหรือมีโรคประจำตัว			
Urinalysis	✓	ปีละ 1 ครั้ง หรือเมื่อมีข้อบ่งชี้	ปีละ 1 ครั้ง หรือเมื่อมีข้อบ่งชี้	• ถ้ามีโรคประจำตัว เช่น เบาหวาน ความดันโลหิตสูง อายุมากกว่า 50 ปี หรือเคยได้ IDV ควรตรวจทุก 6 เดือน • ทุกรายที่ได้ TDF หรือกำลังได้ IDV ควรตรวจทุก 6 เดือน

General principles of management of antiretroviral drug toxicity

- Drug initiation
  - Start drugs with non-overlapping toxicities and small risk of interaction with existing therapy
- Adverse reaction
  - Dose reductions not advised because of potential for drug resistance
  - In patients with good control HIV replication
    - If possible, immediately switch to drug with different toxicity profile (if aetiology certain)
    - Stop all drugs, particularly if severe reaction, then consider new regimen with different toxicity profile (if aetiology uncertain)
  - In patients with uncontrollable HIV replication
    - Stop responsible drug; initiate new agent with different toxicity profile (but if possible aim for new regimen with improved antiviral activity)

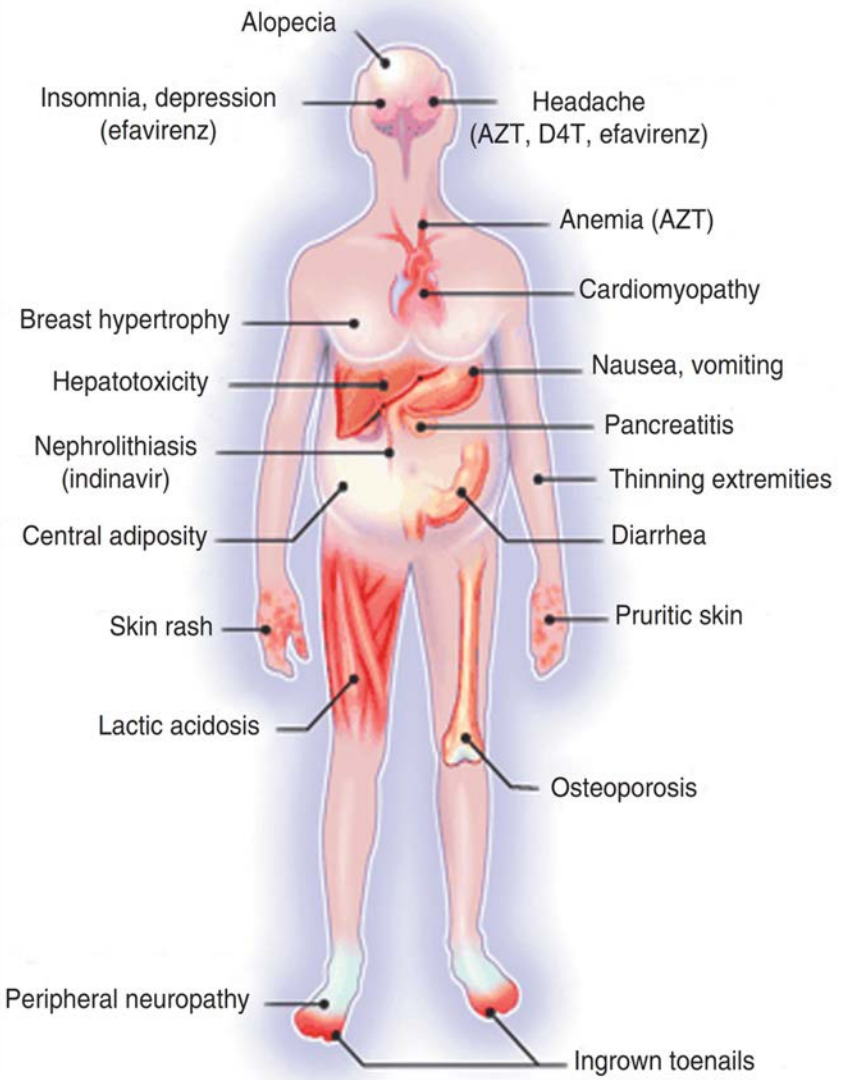
General principles of management of antiretroviral drug toxicity

- **Post adverse reaction**
  - Rechallenge should be medically supervised but is contraindicated with hypersensitivity to:
    - Abacavir (absolute contraindication in HSR)
    - Nevirapine 200 mg/day dose
    - Mucosal involvement
    - Grade 3–4 rash
  - Desensitisation probably inappropriate because of potential for induction of viral resistance

Adverse Event	ARV Agent(s)/Drug Class	
	Switch from	Switch to
Bone Density Effects	TDF[a]	ABC[b]
Bone Marrow Suppression	ZDV	TDF or ABC[b]
Central Nervous System/ Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression	EFV	Alternative NNRTI (RPV, ETR, NVP), a PI/c or PI/r, or an INSTI
Dyslipidemia Hypertriglyceridemia (with or without elevated low-density LDL level)	RTV- or COBI-boosted regimens or EFV	RAL, DTG, RPV, NVP, or unboosted ATV[c]
Gastrointestinal Effects Nausea, diarrhea	LPV/r	ATV/c, ATV/r, DRV/c, DRV/r, RAL, DTG, EVG/c/TDF/FTC
	Other RTV- or COBI-boosted regimens	RAL, DTG, unboosted ATV,[c] NNRTIs
Hypersensitivity Reaction	ABC	TDF
	NVP, EFV, ETR, RPV	Non-NNRTI ART
	DTG, RAL MVC	Non-INSTI ART Suitable alternative ART
Insulin Resistance	LPV/r, FPV/r	NNRTI (NVP or RPV), INSTI, unboosted ATV[c]
Jaundice and Icterus	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI

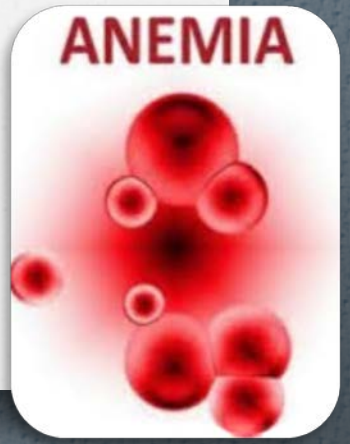
Adverse Event	ARV Agent(s)/Drug Class	
	Switch from	Switch to
Lipoatrophy Subcutaneous fat wasting of limbs, face, buttocks	d4T, ZDV	TDF or ABC[b]
Lipohypertrophy	Accumulation of visceral, truncal, dorso-cervical during use of older PI-based regimens (e.g., IDV remains unclear. There is no clinical evidence th or visceral fat gain.	
Rash	NNRTIs (especially NVP and EFV)	PI- or INSTI-based regimen
	DRV/c, DRV/r	ATV/c, ATV/r or another drug class (e.g., INSTI)
Renal Effects Including proximal renal tubulopathy, elevated creatinine	TDF[a]	ABC[b]
	ATV/c, ATV/r, LPV/r	DTG, RAL, or NNRTI
Stones Nephrolithiasis and cholelithiasis	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI

Complication of ART: Syndrome or Organ-Specific Toxicities



Bone marrow suppression

- Anemia or neutropenia
- Most common associated with zidovudine (AZT)
  - Anemia may occur within 4-6 weeks
  - Neutropenia is usually seen after 12-24 weeks
- **Risk:**
  - Low marrow reserve (Not start AZT when Hb<8 or Hct<24%)
  - High- dose AZT
  - Duration of therapy
  - Advanced HIV (CD4 ≤ 200)
  - Concomitant with myelosuppression drugs (TMP-SMX, dilantin, ribavirin or ganciclovir)



MANAGEMENT
Bone marrow suppression

- Find other causes of anemia and correcting underlying metabolic disorders
- Folic acid supplement or blood transfusions
- Switch AZT → TDF, ABC or d4T
- Consider G-CSF for neutropenia or erythropoietin for anemia

Gastrointestinal toxicities

- **Nausea, vomiting and diarrhea** were the major reasons for discontinuation in the acute phase of treatment
- NRIs (AZT>ABC> TDF)
- NNRTIs have relatively few GI adverse effects
- PIs : LPV/r> DRV/r and ATV/r
- (GI toxicity is one of the main treatment limiting AEs for this class of drugs.)
- Integrase inhibitors and entry inhibitors (fusion inhibitors and CCR5 receptor blockers) have not generally been associated with GI AEs

MANAGEMENT GI toxicity

- Evaluation of other causes: opportunistic infection or malignancy
  - **Nausea/vomiting**
    - Intracranial infection/tumor: meningitis, abscess or lymphoma
    - Esophageal infection: candida, Herpes, CMV
    - Esophagitis, gastritis
  - **Diarrhea**
    - TB/NTM
    - CMV
    - Lymphoma
    - Parasite/protozoa
    - Ulcerative colitis

MANAGEMENT GI toxicity

- **For nausea/vomiting :** supportive or pharmacologic
  - patient education
  - advice and support
  - medications with meals (except ddI)
  - nutritional counseling.
  - Pharmacologic treatment includes antiemetic agents, acid reducing agents or switching medications
- **For diarrhea :**supportive or pharmacologic
  - nutritional counseling, for example to increase fiber in the diet and reduce the use of refined foods.
  - Pharmacologic intervention may include the use of antidiarrheal agents or involve switching medications

Hepatic adverse effects

- **Risk : viral hepatitis coinfection, concomitant with hepatotoxic drugs (anti-TB or azole)**
- **Most NRTIs:** AZT, d4T and ddI→ hepatitis
  - ddI: prolonged exposure linked to non-cirrhotic portal hypertension and esophageal varices
  - In patients with HIV-HBV coinfection, hepatits may flare upon discontinuation of FTC, 3TC or TDF
- **NNRTIS:** NVP > other NNRTIs
  - NVP: severe hepatotoxicity associated with skin rash or HSR→ 2 weeks NVP-lead in may reduce risk and risk greater for women CD4>250 and men CD4>400
  - NVP should never be used for PEP, or in patients with hepatic insufficiency (child-Pugh B or C)

Hepatic adverse effects

- **PIs:** all drugs induce hepatitis and hepatic decompensated
  - IDV, ATV : jaundice due to indirect hyperbilirubinemia
- **MVC:** hepatotoxicity with or without rash

Renal complication in HIV

HIV infection

HIVAN: defined by

- renal biopsy (focal and segmental glomerulosclerosis) and
- clinical criteria (nephrogenic proteinuria, increased echogenic of kidney, lack of hypertension or relevant edema, and progressive renal failure), black population

HAART

Complication from others treatment: amphotericin B, NSAID,herbal use

Renal complication

Table 1. Predominant renal involvement in HIV-infected patients

Class of nephropathy	Specific disease	Pathogenetic and histologic aspects
Glomerular diseases	HIVAN	Focal and segmental glomerulosclerosis, "collapsing variant"
	Immune complex GN	Mesangial proliferative GN with IgA immune deposits (secondary IgA nephropathy) or diffuse proliferative GN with IgG, IgM, C3 and C1q immune deposits (Lupus-like proliferative GN)
	Other GN	Membranous GN or membranoproliferative GN, immunotactoid GN
Vascular nephropathy	Hemolytic-uremic syndrome	Microangiopathy, hyaline glomerular thrombi, necrosis, swollen glomerular endothelium
Tubulointerstitial nephritis	Acute or chronic TIN	Hypersensitivity reactions to drugs: tubulitis, marked interstitial leukocyte infiltration, fibrosis, tubular atrophy Drug toxicity: tubular atrophy, Fanconi's syndrome
Acute kidney injury	Acute drug (antiretroviral or antibiotics) toxicity, sepsis, rhabdomyolysis	Toxic acute tubular necrosis

HIVAN: HIV-associated nephropathy; GN: glomerular neuropathy; TIN: tubulointerstitial nephritis.

AIDS Reviews. 2012;14

classes	ARV	Renal adverse effects
NRTIs	Abacavir	Acute interstitial nephritis
	Didanosine	Lactic acidosis, Acute renal failure, nephrogenic diabetes insipidus, Fanconi syndrome
	Lamivudine, Stavudine	Renal tubular acidosis, hypophosphatemia (case report)
NtRTI	Tenofovir	Proximal tubulopathy with Fanconi syndrome, Acute renal failure, nephrogenic diabetes insipidus,
NNRTIs	Efavirenz	Nephrolithiasis
PIs	Indinavir	Cystalluria, nephrolithiasis, dysuria, acute interstitial nephritis with cystalline casts in tubules, and papillary necrosis, renal atrophy, acute and chronic renal failure
	Ritonavir	Acute renal failure
	Atazanavir	Acute interstitial nephritis, nephrolithiasis
	Saquinavir	Renal calculi
	Nelfinavir	Nephrolithiaisis (case report)
Fusion inhibitor	Enfuvirtide	Membranoproliferative glomerulonephritis (case report)

Box 2 | Guidelines for screening patients with HIV for pre-existing renal disease[57]

- Upon HIV diagnosis, patients should be assessed for pre-existing kidney disease by use of urinalysis and calculation of estimated GFR; patients with 1+ proteinuria or GFR <60 ml/min/1.73 m^2 should be referred to a nephrologist
- Patients with diabetes must be tested for microalbuminuria (defined as an albumin to creatinine ratio 30–300 mg/mg), a range not detected using conventional urine dipsticks
- Additional evaluations (e.g. quantification of proteinuria and renal ultrasonography) should be implemented on a case-by-case basis
- Patients at high risk of kidney disease (i.e. black patients, patients with $CD4^+$ T-cell count <200 cells/mm^3, HIV RNA levels >4,000 copies/ml, diabetes, hypertension, or HCV coinfection) should be screened at least annually for subtle changes in renal parameters; patients on tenofovir might need to be monitored every 3 months[104]
- A kidney biopsy is recommended for patients with unexplained kidney disease, especially those with heavy proteinuria or reduced GFR, because they are at the greatest risk of ESRD

Abbreviations: ESRD, end-stage renal disease; GFR, glomerular filtration rate; HAART, highly active antiretroviral therapy.

TDF-induce kidney disease

- Mostly including acute proximal tubulopathy with Fanconi's syndrome lead to Ca and PO4 dysregulation, acute renal failure, osteomalacia and fracture) and nephrogrnic diabetes insipidus (DI))
  - Increase serum Cr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hyperuricosuria, hypokalemia, non-anion gap metabolic acidosis

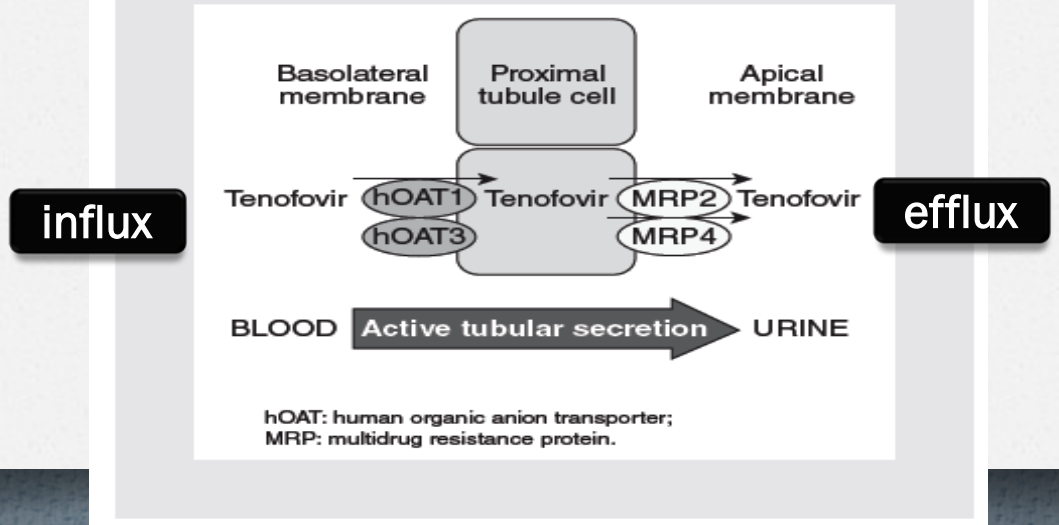


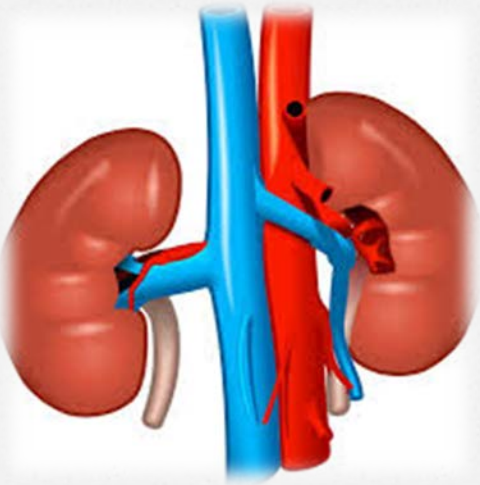
Figure 1. *Proposed mechanism of active tubular secretion of tenofovir.*

TDF-induce kidney disease

- Predictor of tubular dysfunction
  - Increased age
  - Low body weight
  - Comorbid: pre-existing renal disease, DM , HT
  - Higher TDF plasma level
  - Concomitant use of ddI or ritonavir boosted PI
  - Concomitant receipt of nephrotoxic drugs
  - Polymorphisms in genes: genotype CC (than CT and TT) at position -24 of ABCC2 gene encoding the cellular transporter MRP2

Renal adverse effects

- **PIs** : ATV and LPV/r : increased chronic kidney disease
  - IDV: increased serum Cr, pyuria, renal atrophy or hydronephrosis
  - IDV,ATV: stone, crystal formation, adequate hydration (1.5-2 L/day) may reduce risk
- **Cobicistat** (in EVG/c/TDF/FTC) and DTG: inhibit Cr secretion without reducing renal GFR



Box 3 | Recommendations for tenofovir use in patients with CKD[57]

Screening for tenofovir-induced tubular dysfunction should be carried out in the following situations:

- GFR <90 ml/min/1.73 m^2
- Use of other medications eliminated via renal secretion (e.g. adefovir, acyclovir,

การตรวจทางห้องปฏิบัติการ	เมื่อทราบว่าติดเชื้อครั้งแรก	ในปีแรก	ในปีต่อๆ ไป	หมายเหตุ
Creatinine	✓	ที่ 6 และ 12 เดือน	ปีละ 1 ครั้ง หรือเมื่อมีข้อบ่งชี้	• ถ้ามีโรคประจำตัว เช่น เบาหวาน ความดันโลหิตสูง อายุมากกว่า 50 ปี น้ำหนักตัวน้อยกว่า 50 kg หรือเคยได้ IDV ควรตรวจทุก 6 เดือน • ในทุกรายที่ได้ TDF หรือกำลังได้ IDV ควรตรวจทุก 6 เดือน
Urinalysis	✓	ปีละ 1 ครั้ง หรือเมื่อมีข้อบ่งชี้	ปีละ 1 ครั้ง หรือเมื่อมีข้อบ่งชี้	• ถ้ามีโรคประจำตัว เช่น เบาหวาน ความดันโลหิตสูง อายุมากกว่า 50 ปี หรือเคยได้ IDV ควรตรวจทุก 6 เดือน • ทุกรายที่ได้ TDF หรือกำลังได้ IDV ควรตรวจทุก 6 เดือน

nondiabetic glycosuria

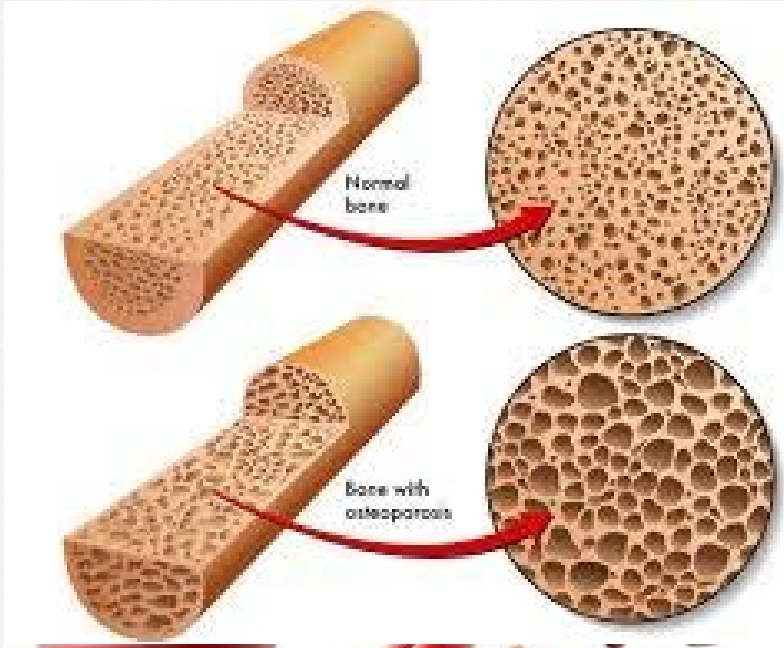
Tenofovir dose adjustment is recommended when estimated GFR <60 ml/min/1.73 m^2

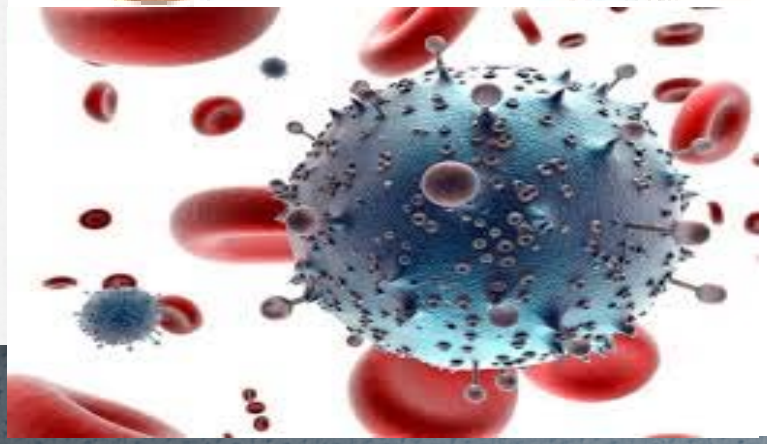
*Renal function and potential tubular abnormalities should be monitored at least twice a year. Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

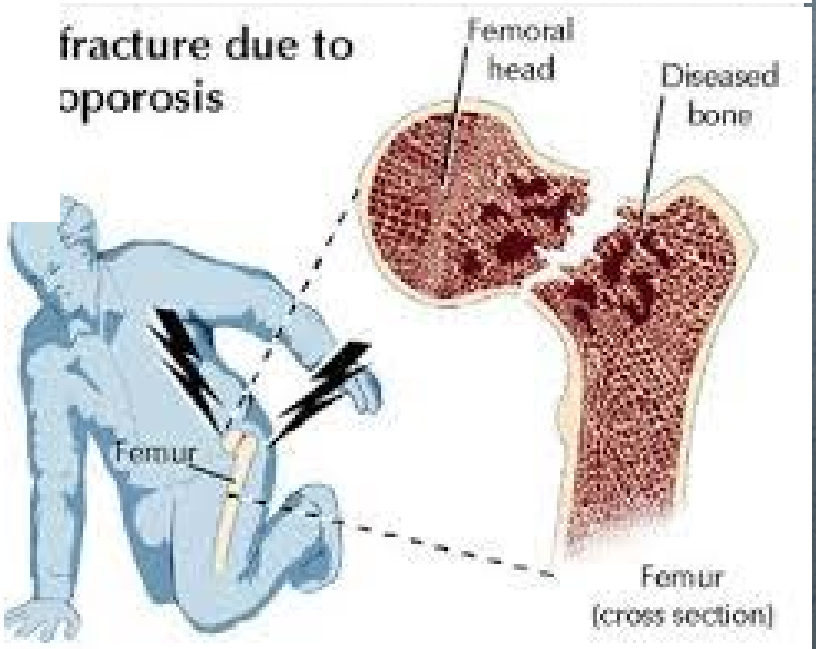
Management Renal adverse effects

- Stop causatic ARV and switch to other ARV
  - Renal effect:
    - TDF→ ABC
    - ATV, LPV/r → DTG, RAL, or NNRTI
  - Stones: ATV→ DRV, INSTI, or NNRTI
- Supportive care and correct electrolyte imbalance

Bone Loss: Host Factors, ARV, or HIV disease?





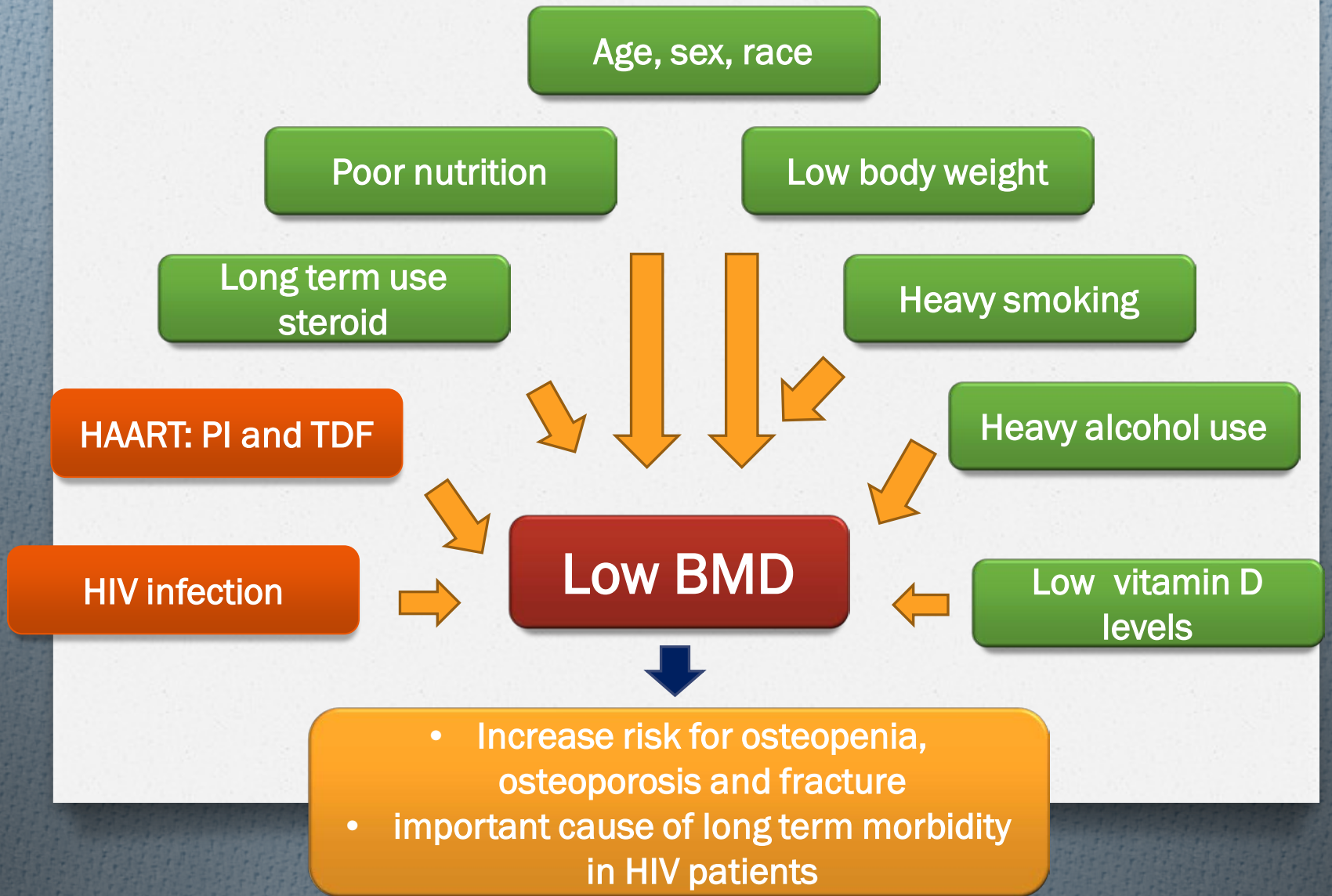


HIV Bone disorder

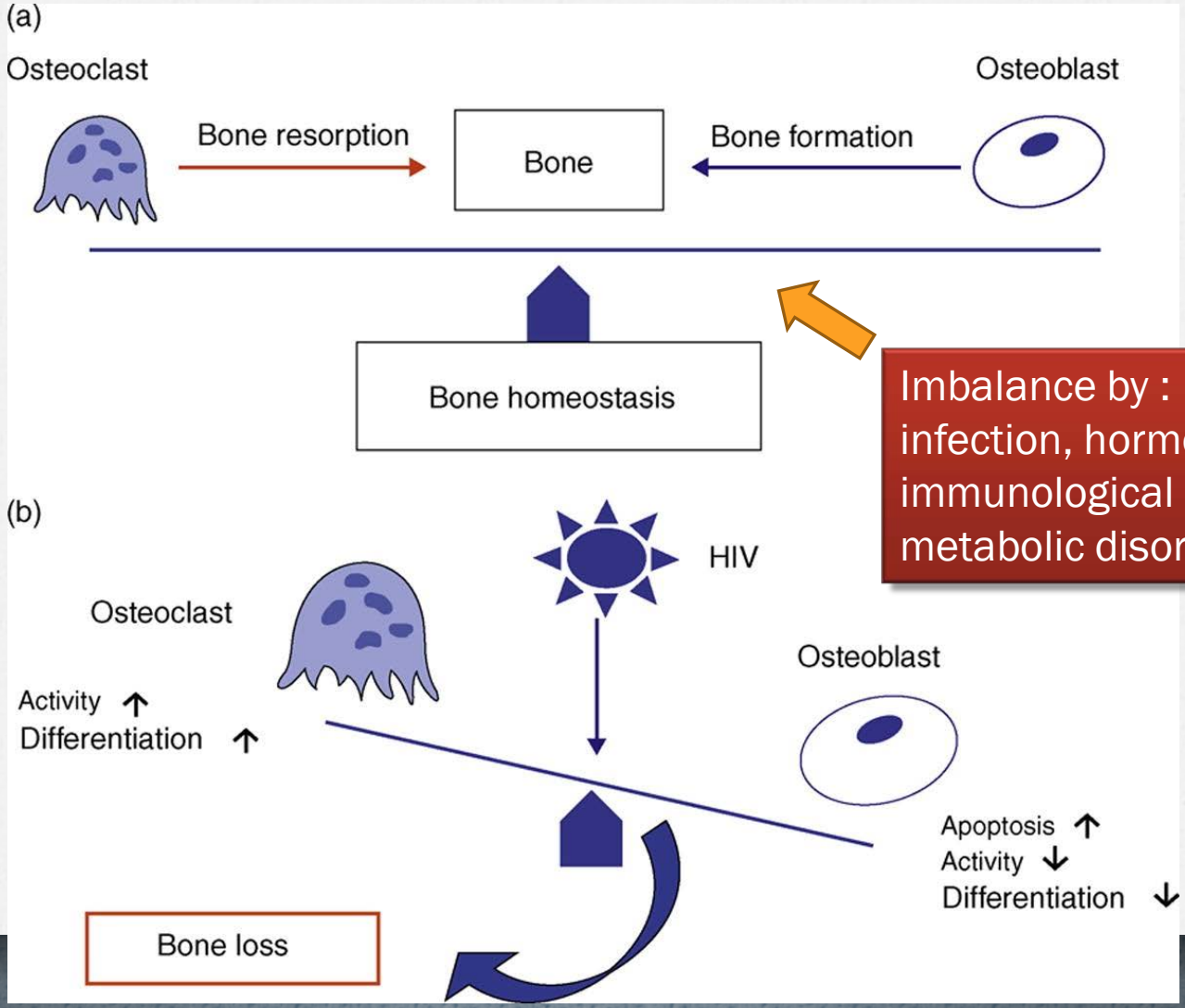
- The major bone lesions detectable in HIV patients are related to bone demineralization (osteopenia (3.7 fold)/osteoporosis (6.4 fold) and osteomalacia) and osteonecrosis
- Reduced BMD is the most common bone lesion found in HIV
- BMD is a parameter that predicts fracture risk
- BMD is measured by the dual X-ray absorptiometry scan (DXA)

Bone disorder	Definition
Osteopenia	Bone mineral density reduction
Osteoporosis	Bone strength reduction with increased fracture risk
Osteomalacia	Softening of the bones due to defective bone mineralization
Osteonecrosis	Bone death due to poor blood supply

Bone Loss in HIV



Mechanisms of HIV-associated osteopenia/osteoporosis

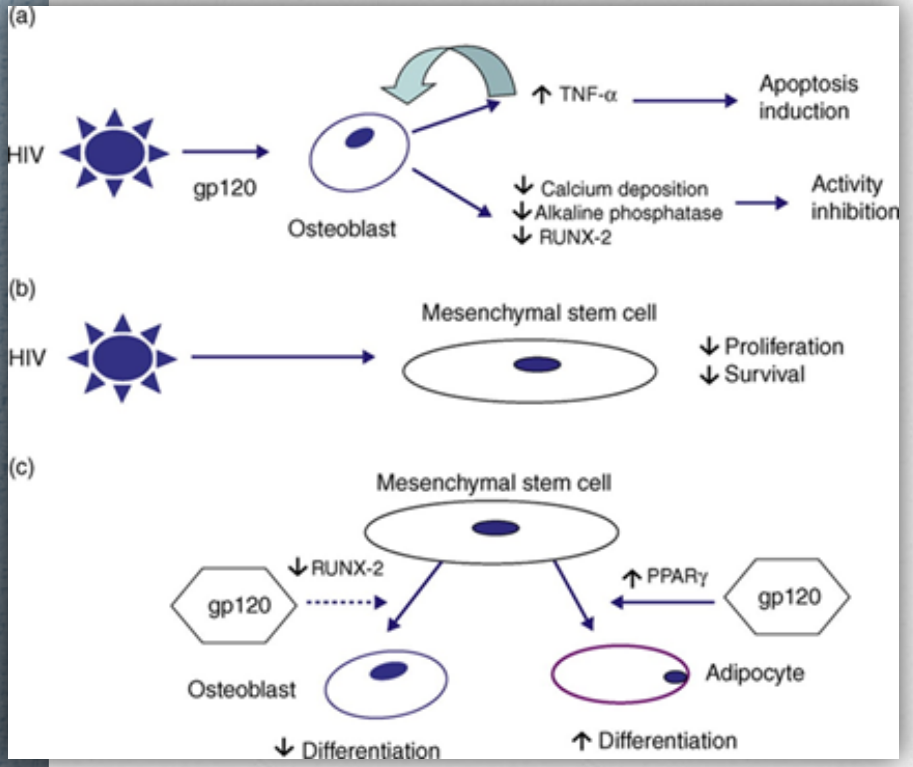


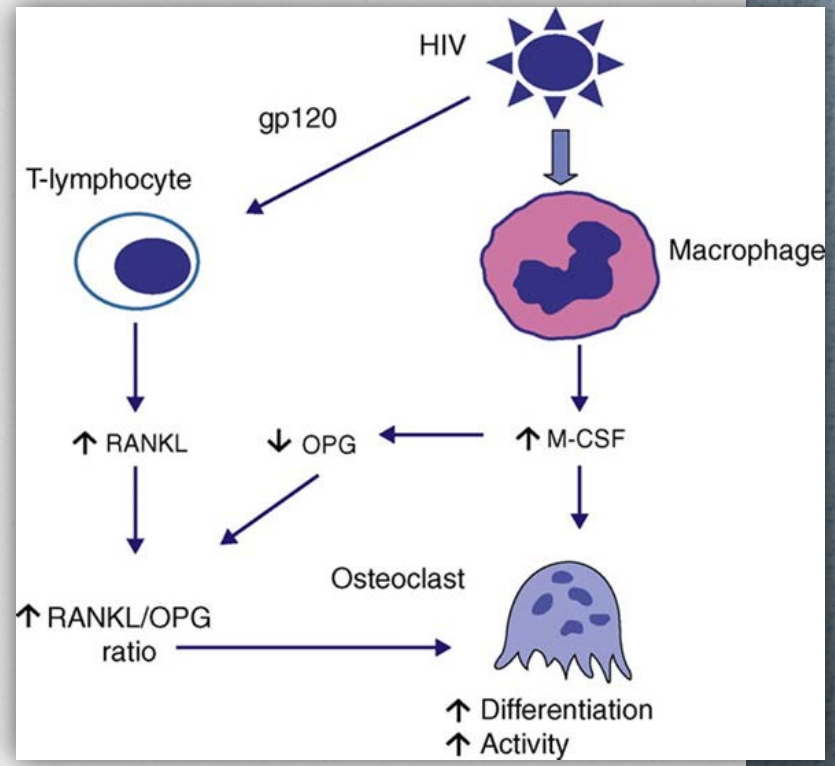
Osteoblast : bone rebuilding

- Increase apoptosis
- Decrease activity and differentiation

Osteoclast : bone resorption

Increase activity and differentiation



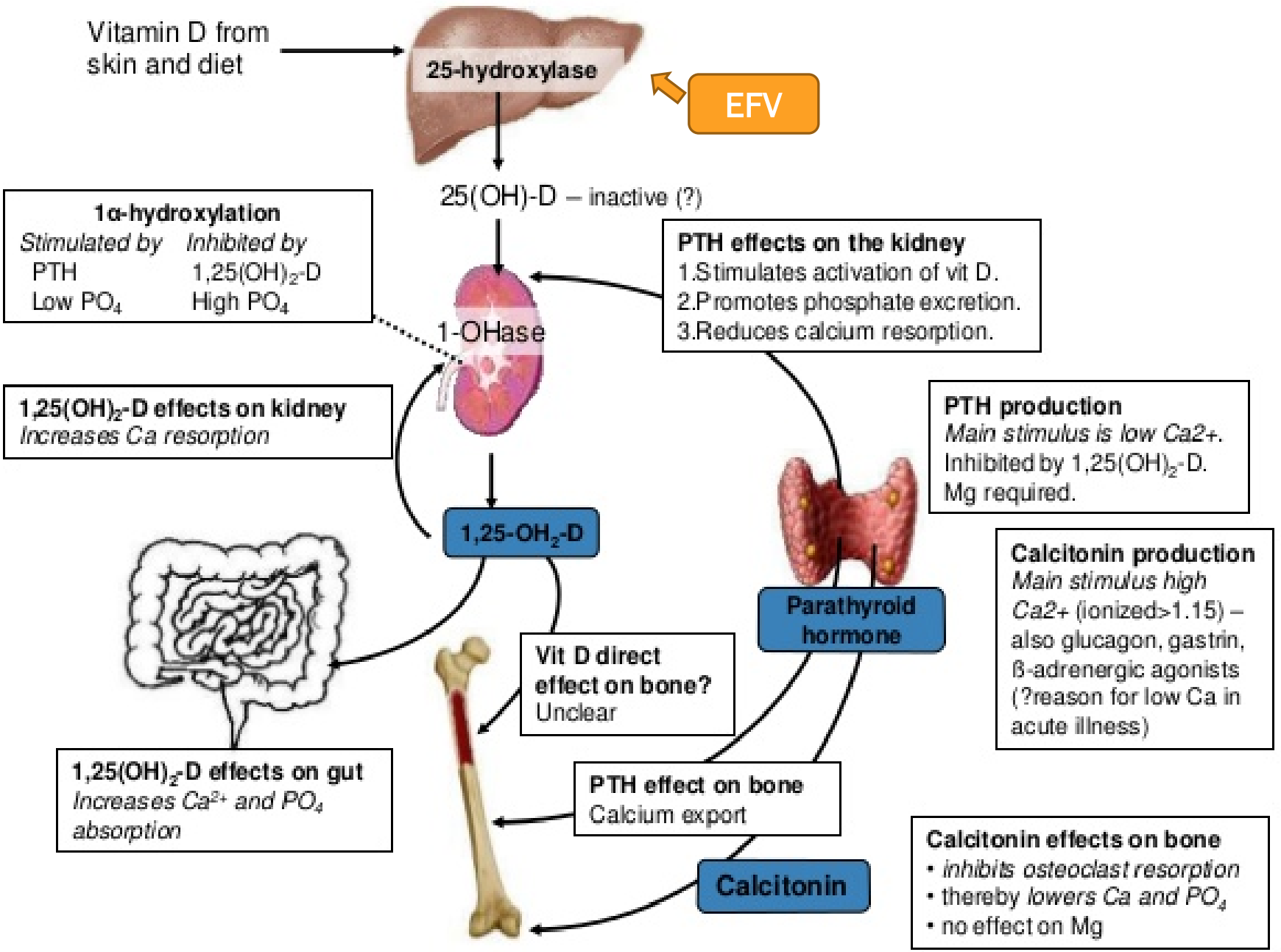


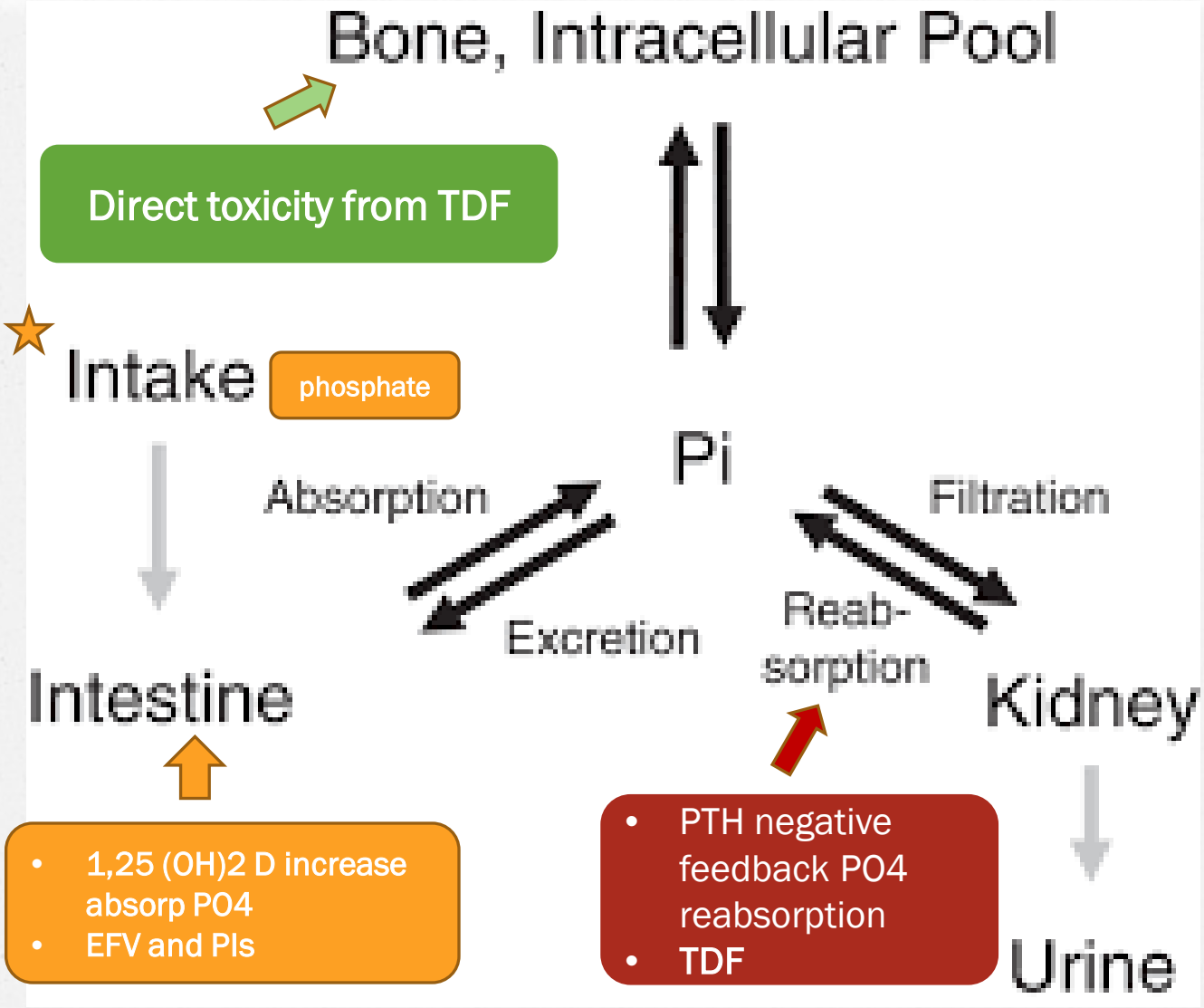
HAART effect to Bone loss

ARV class	ARV drug	Effect	Mechanism
NRTIs	ddI, d4T	Softening of bone matrix	Calcium mobilization to compensate hyperlactemia (lactic acidosis)
	AZT	Increased osteoclastogenesis	Enhancing of RANKL-mediated osteoclastogenesis
	TDF	Vitamin D deficiency and hypophosphatemia	nephrotoxicity
NNRTIs	EFV	Decreased active vitamin D (25 (OH) D)	
PIs	SQV, RTV	Enhancement of osteoclastogenesis	Abrongation of IFN-y-mediated RANKL inhibition
	IDV, RTV	Impaired osteoblastic activity	Reduction of calcium deposition and bone alkaline phosphate activity
	RTV, IDV, NFV	Vitamin D deficiency	Inhibit of 1-∞-hydroxilase and 25-hydroxilase enzyme

TDF: associated with greater loss of BMD than other NRTIs

AIDS. 23(11):1297-1310, July 17, 2009.


Vitamin D from skin and diet
25-hydroxylase
EFV
25(OH)-D – inactive (?)
1α-hydroxylation
Stimulated by PTH
Stimulated by Low PO4
Inhibited by 1,25(OH)2-D
Inhibited by High PO4
1-OHase
PTH effects on the kidney
1.Stimulates activation of vit D.
2.Promotes phosphate excretion.
3.Reduces calcium resorption.
1,25(OH)2-D effects on kidney
Increases Ca resorption
PTH production
Main stimulus is low Ca2+.
Inhibited by 1,25(OH)2-D.
Mg required.
1,25-OH2-D
Parathyroid hormone
Calcitonin production
Main stimulus high Ca2+ (ionized>1.15) – also glucagon, gastrin, ß-adrenergic agonists (?reason for low Ca in acute illness)
Vit D direct effect on bone?
Unclear
1,25(OH)2-D effects on gut
Increases Ca2+ and PO4 absorption
PTH effect on bone
Calcium export
Calcitonin
Calcitonin effects on bone
• inhibits osteoclast resorption
• thereby lowers Ca and PO4
• no effect on Mg


Bone, Intracellular Pool
Direct toxicity from TDF
Intake
phosphate
Pi
Absorption
Excretion
Filtration
Reab-
sorption
Intestine
Kidney
Urine
1,25 (OH)2 D increase absorp PO4
EFV and PIs
PTH negative feedback PO4 reabsorption
TDF

Causes of Secondary Osteoporosis

Osteoporosis-Associated Condition	Laboratory Evaluation
Endocrine disorders	
Vitamin D deficiency[a]	25-hydroxy vitamin D
Hyperparathyroidism[a]	Intact parathyroid hormone, total calcium, phosphate, albumin, creatinine
Subclinical hyperthyroidism[a]	Thyroid-stimulating hormone, free thyroxine
Hypogonadism[a]	Men: free testosterone with morning measurement; women: menstrual history, estradiol, follicle-stimulating hormone, prolactin
Cushing syndrome	1 mg overnight dexamethasone suppression test or late-evening salivary cortisol levels
Renal disorders	
Phosphate wasting[a]	Simultaneous serum phosphate and creatinine and spot urine phosphate and creatinine to calculate fractional excretion of phosphate
Idiopathic hypercalcuria[a]	24-hour urinary calcium
Gastrointestinal disorders	
Celiac sprue	Immunoglobulin A tissue transglutaminase antibody
Hematologic disorders	
Multiple myeloma	Complete blood count, serum protein electrophoresis
Mastocytosis	Serum tryptase

Recommendations for Evaluation and Management of Bone Disease in HIV

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- guidance and recommendations on the **screening, diagnosis, monitoring, and management** of bone disease in patients with HIV

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Screening and Monitoring Individuals With HIV Infection at Risk for Fragility Fracture

- Appropriate to assess the risk of fragility fracture and low BMD in all HIV-infected adults

1. Patients with **major risk factors** for fragility fracture, including
   (1) Previous history of fragility fracture
   (2) receipt of glucocorticoid treatment for >3 months (≥5 mg of prednisone daily or equivalent)
   (3) High risk for Falls

   should be evaluated with DEXA
2. In patients **without major fracture** risk factors, an age-specific evaluation is appropriate

Fracture Risk Assessment by Fracture Risk Assessment Tool (FRAX)

- Patients **without a major risk factor**
  - men who are aged 40–49 years and
  - premenopausal women aged ≥40 years should have their 10-year risk of fracture assessed using the Fracture Risk Assessment Tool (FRAX score) without BMD
- FRAX gives a calculation of the 10-year probability of a major fracture (spine, forearm, proximal humerus, or hip) or hip fracture alone and can be used with or without BMD assessment
- Risk assessment performed every 2–3 years or when a new clinical risk factor develops

Risk factors required for FRAX

✓ Age
✓ Race/geographic location
✓ Female sex
✓ BMI/height and weight
✓ Prior fragility fracture
✓ Parental history of hip fracture
✓ Current tobacco smoking
✓ Alcohol ≥3 standard drinks per day
✓ Long-term use of glucocorticoids (≥5 mg prednisone per day or equivalent for >3 mo)
✓ Rheumatoid arthritis
✓ Secondary causes of osteoporosis[a]
✓ Additional risk factors important for fracture risk assessment
✓ Frailty/fall risk/physical inactivity
✓ Vitamin D deficiency

[a] Includes type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years of age), chronic malnutrition, or malabsorption and chronic liver disease.

Fracture Risk Assessment by Fracture Risk Assessment Tool (FRAX)

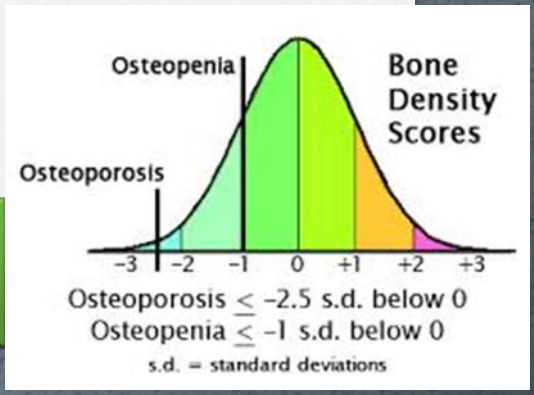
Table 2. Interpretation of Fracture Risk Assessment Tool Scores

Fracture Risk	Definition	Management
Low	<10% 10-year risk of major fracture	Reassure and reassess in ≤5 y depending on the clinical context
Moderate/intermediate	10%–20% 10-year risk of major osteoporotic fracture	Measure BMD and recalculate fracture risk to determine whether an individual's risk lies above or below the intervention threshold
High	10-year risk of major osteoporotic fracture ≥20% and/or hip fracture ≥3%	Can be considered for treatment without the need for BMD, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women

DXA Screening

- Reasonable to assess BMD by DXA scans in
  (1) men aged 40–49 years or premenopausal women aged ≥40 years, who have an **intermediate- or high-risk** stratification by FRAX (>10% 10-year risk of major osteoporotic fracture)
  (2) all postmenopausal women
  (3) all men ≥50 years of age
  (4) adults with major fragility fracture risk factors regardless of age

Routine DXA screening of all HIV-infected patients on ART is not recommended



Bone Mineral Density T- and Z-Score Thresholds for Determination of Osteopenia and Osteoporosis

Population	Interpretation: Use of T-Score or Z-Score	Normal	Osteopenia	Osteoporosis
Postmenopausal women and men ≥50 y of age	T-score (compared with a young healthy adult)	≥ −1 SD	Between −2.5 and −1 SD	≤ −2.5 SD
All others aged less than 50 years	Z-score (age-, sex-, ethnicity-matched)	Low BMD for chronological age if ≤ −2 SD		

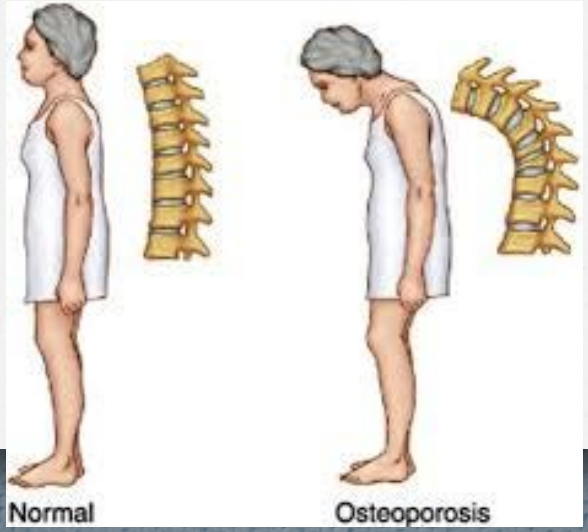
- [a] In premenopausal women, men <50 years of age, and children, the diagnosis of osteoporosis should not be made by BMD criteria alone
- Z-score has no clear cut-off value for osteopenia and osteoporosis and the following scores are recommended: patients with values lower than −1 are classified as having low bone mass, whereas a severe bone mass reduction is identified by Z-score values lower than −2

DEXA Screening

- The optimal interval between DXA scan screening (or FRAX assessment) is unknown.
- Repeat DXA scanning should be considered
  - After 1–2 years for those with baseline advanced osteopenia (T-score, −2.00 to −2.49)
  - After 5 years for mild to moderate osteopenia (Tscore, −1.01 to −1.99)

Vertebral Fracture Screening and Assessment

- Subclinical vertebral fractures are common in HIV-infected individuals (prevalence approximately 25%) and are a strong risk factor for future fractures.
- Therefore, height should be measured every 1–2 years in adults ≥50 years of age



Vertebral Fracture Screening and Assessment

- Assessment by using lateral X-rays of the L-spine and T-spine or DXA-based Vertebral Fracture Assessment is indicated for:
  - women ≥70 years of age and all men ≥80 years of age if BMD T-score is < –1.0 at the spine, total hip or femoral neck
  - women 65–69 years of age, and men 75–79 years of age, if BMD T-score is < –1.5
  - postmenopausal women 50–64 years of age and men 50–69 years of age with specific risk factors such as fragility fracture, historical height loss of ≥4 cm (≥1.5 inches), prospective height loss of ≥2 cm (≥0.8 inches), or recent or ongoing long-term glucocorticoid treatment

Managing ART in ART-Naive and -Experienced Patients

- Discussion about alternative ART regimens should occur in treatment-naive or -experienced individuals with low BMD or osteoporosis
- Avoidance of TDF or boosted PIs, as these regimens have been associated with a greater decrease in BMD compared with other NRTIs and RAL .
- Novel ARV such as a ritonavir-boosted PI plus raltegravir have been associated with significantly smaller changes in BMD than a ritonavir-boosted PI plus TDF/FTC regimen
- Dolutegravir plus ABC/3TC is a recommended regimen; however, there are no published data on the effects of dolutegravir on BMD

Optimal management strategy for patients at risk for fragility fracture

- Reminded to increase regular weight-bearing and muscle strengthening exercise, avoid tobacco use and excessive alcohol intake, and take steps to prevent falls
- Dietary and lifestyle changes
  - Adequate daily intake of dietary calcium is recommended for postmenopausal women and men ≥ 50 years of age
  - Daily total calcium intake should be
    - 1000 mg for men 50–70 years of age, or
    - 1200 mg for women ≥ 51 years of age and men ≥ 71 years of age
  - Calcium supplements may be appropriate if dietary calcium intake is insufficient

Vitamin D supplement

- HIV-infected patients are at risk of vitamin D insufficiency or deficiency
- Vitamin D status should be determined by **serum 25-hydroxy vitamin D levels** in those with a history of low BMD and/or fracture
- Determination of vitamin D status may also be considered in patients with any of the major risk factors for low vitamin D levels eg,
  - dark skin
  - dietary deficiency
  - avoidance of sun exposure
  - Malabsorption
  - Obesity
  - chronic kidney disease
  - treatment with regimens containing efavirenz

Vitamin D supplement

- Supplementary vitamin D should be given to HIV-infected patients with vitamin D insufficiency (<20 ng/mL [<50 nmol/ L]) or deficiency (<10 ng/mL [<25 nmol/L]), particularly if the deficiency is associated with compensator hyperparathyroidism
- Vitamin D intake should be titrated to achieve a serum 25-hydroxy vitamin D level of approximately 30 ng/mL (75 nmol/L) and a suitabl maintenance dose administered thereafter to sustain this level
- Vitamin D deficiency can blunt bone response to bisphosphonate treatment
  - target serum 25-hydroxy vitamin D level of 30 ng/mL should be achieved before initiating therapy with an antiresorptive drug

Table 6. Vitamin D Supplementation Regimens[a]

Vitamin D Level	Supplementation Regimen
>30 ng/mL (75 nmol/L)	1000 IU/day vitamin D3 (cholecalciferol)
20–30 ng/mL (50–75 nmol/L) (insufficiency)	2000 IU/day vitamin D3
15–19 ng/mL (37.5–50 nmol/L) (deficiency)	Vitamin D2 (ergocalciferol) or D3 50 000 IU/week × 8 weeks (or equivalent of 6000 IU/day vitamin D3)[b]
	Maintenance: vitamin D3 2000 IU/day[c]
<15 ng/mL (37.5 mmol/L) (severe deficiency)	Vitamin D2 or D3 50 000 IU once weekly × 8–12 wk (or equivalent of 6000 IU/day vitamin D3)[b]
	Maintenance: vitamin D3 2000 IU/day[c]

Source: [15].

[a] Well-designed trials investigating the effects of calcium and vitamin D on bone mineral density in human immunodeficiency virus–positive individuals are still lacking.

[b] Consider a more aggressive replacement strategy if patient has secondary hyperparathyroidism, osteomalacia, malabsorption syndrome, or obesity or is taking medications that affect vitamin D metabolism.

[c] Recheck 25-hydroxy vitamin D level after course of ergocalciferol, with a goal of >30 ng/mL. Consider monitoring urinary calcium in patients with a history of nephrolithiasis and concurrent calcium supplementation.

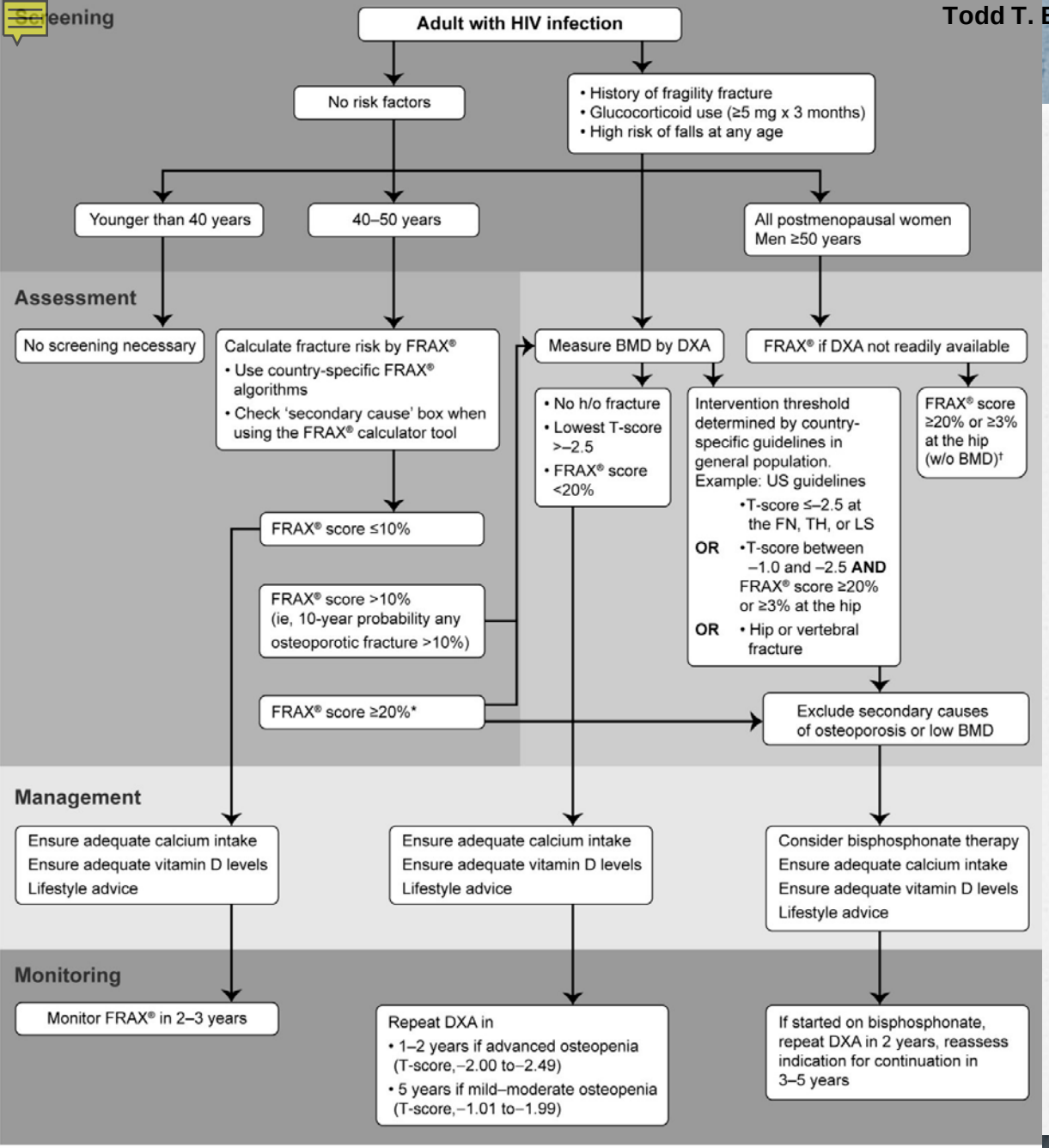
Therapeutic Management of Osteoporosis in HIV-Infected Patients

- Anti-osteoporosis treatment should be initiated for HIV-infected patients under the same criteria as general population
  - Alendronate (70 mg once weekly with calcium carbonate 1000 mg/vitamin D 400 IU per day) or zoledronic acid (IV 5 mg yearly) recommended for HIV infected patients with osteoporosis
- Avoidance or discontinuation of medications associated with bone loss eg,
  - antiepileptic drugs
  - proton pump inhibitors
  - Thiazolidinediones
  - corticosteroids

Todd T. Brown et al. Clin Infect Dis. 2015;cid.civ010

Clinical Infectious Diseases

Algorithm for the screening, assessment, management, and monitoring of bone disease in human immunodeficiency virus (HIV)-infected patients.



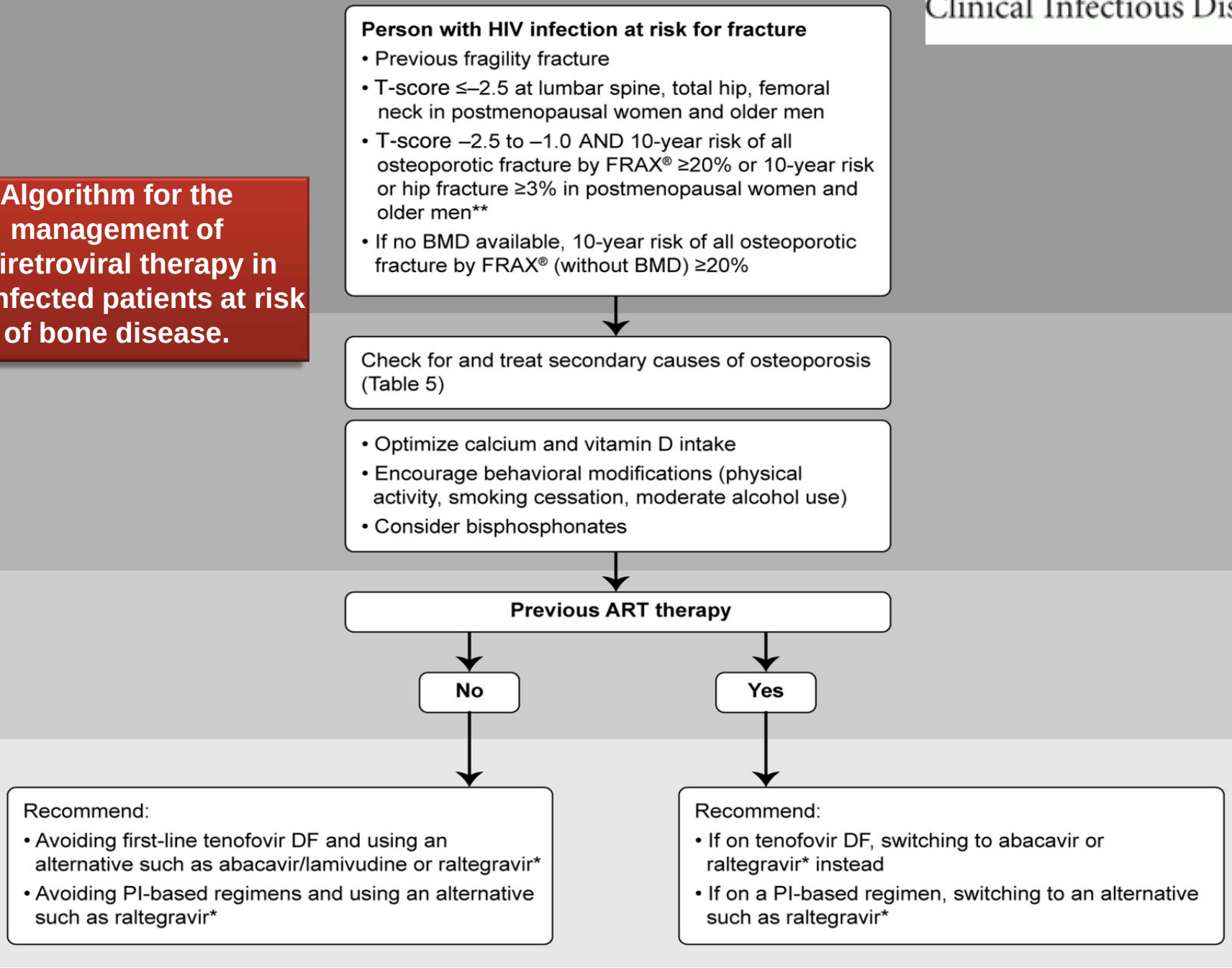
In some countries, persons at high risk of fracture by FRAX® are eligible for further workup/osteoporosis treatment without DXA

Based on US guidelines (National Osteoporosis Foundation). Country-specific intervention thresholds are preferred

T-scores should use the Caucasian young female reference for men and women regardless of ethnicity according to International Society of Clinical Densitometry (http://www.iscd.org/official-positions/2013-iscd-official-positions-adult/)

Clinical Infectious Diseases

Algorithm for the management of antiretroviral therapy in HIV-infected patients at risk of bone disease.



*There are limited to no data for the other integrase inhibitors **Based on US intervention thresholds. Country-specific guidelines should apply.

Drug-related skin rashes

- 100 times more common in HIV-positive patients than in the general population
- Typically manifests as an erythematous, maculopapular, pruritic, and confluent rash (most prominent on the body and arms) with or without fever
- usually begins after 1–3 weeks therapy
- Most commonly drugs:
  - ART: NVP EFV, ABC and ATV
  - Antibiotics: sulphonamide (TMP-SMX) occur in up to 30% of patients , anti-TB
  - Anticonvulsant: carbamazepine, phenobarbital, and phenytoin are associated with DRESS syndrome, usually occuring 2-8 weeks following drug initiation

Drug-related skin rashes

- Especially crucial if the rash is associated with:
  - ❖ Fever
  - ❖ Blistering
  - ❖ Facial swelling
  - ❖ Aches

Drug-related skin rashes

1. MP rash

2. Hypersensitivity reaction

Drug rash with eosinophilia and systemic syndrome (DRESS)

3. Steven-Johnson Syndrome (SJS) or Toxic epidermal necrolysis (TEN)

- usually begins up to 8 weeks after exposure
- Classic symptoms: exanthem, fever and involvement of one or more internal organs
  - 50% hepatitis
  - 30% eosinophilia,
  - 10% nephritis or pneumonitis.

SJS: usually manifests 1 to 3 weeks after ART initiation, but can even occur after 6 to 8 weeks, mortality 1%-5%

- flu-like symptoms: fever, malaise, variable gastrointestinal and respiratory symptoms
- MP rash, symmetrically distributed that develops into blisters, but never involves hairy skin on the head.
- mucosal involvement (mouth and oral cavity, conjunctiva, genitals)

TEN : severe form of SJS that occurs when more than 30% of skin surface is involved. Mortality 30%-50%

Hypersensitivity reaction (HSR)

- **Abacavi**r can cause a potentially fatal hypersensitivity reaction
- fever and rash occurred in more than 70% of patients
- 90% of these patients developed symptoms in the first 6 weeks of treatment, and the median time to development of symptoms was 9 days
- The syndrome has been linked to the human leukocyte antigen (HLA) B*5701 allele

ABC-Hypersensitivity reaction (HSR)

- Diagnosis of HSR required two symptoms of the following five symptom complexes:
  1. Fever
  2. Rash (of any type)
     - most often described as ‘‘maculopapular,’’ but descriptions of urticaria, diffuse erythema, erythema multiforme, or targetoid skin lesions
  3. Gastrointestinal disturbances (diarrhea, vomiting, abdominal pain)
  4. Other constitutional complaints (chill,myalgia, headache, malaise, arthralgia)
  5. Respiratory symptoms (cough, dyspnea)

Management ABC-HSR

- Rapid discontinuation of ABC whenever the hypersensitivity syndrome is suspected
  - all the symptoms disappear within 72 hours of discontinuation
- Supportive care with analgesics, antihistamines, oxygen, intravenous fluids, and appropriate laboratory monitoring for liver involvement and peripheral blood count abnormalities is indicated
- Re-introduction of ABC-HSR results in an accelerated anaphylaxis-like reaction that has resulted in rash, urticaria, respiratory compromise, circulatory collapse, and death, sometimes within hours of receiving one dose of ABC

Hypersensitivity reaction (HSR)

- **Nevirapine** →DRESS
  - Most common organ involvement is hepatitis
  - Fever, malaise, fatigue, myalgia, conjunctivitis, facial edema, eosiophillia, lymphadenopathy
  - Risk greater for ARV-naive women with pre-NVP CD4>250 and men with pre-NVP CD4>400
  - Prevention: NVP lead-in 200 mg q 24 h in first 2 weeks and early detection rash

Management skin rash

- Skin rash
  - Mild to moderate : Antihistamine+ continue ARV
- Hypersensitivity reaction
  - About 50% of antiretroviral hypersensitivity resolves spontaneously despite continuation of therapy
  - Reactions may worsen temporarily after cessation of drug therapy, particularly with drugs with longer half-lives.
  - ARV should be stopped if mucosal involvement, blistering, exfoliation, aminotransferase > 3 times , fever greater than 39°C, or intolerable fever or pruritus.
  - The rate of NNRTI cross-hypersenstivity is not known, so new NNRTI therapy in patients with prior severe hypersensitivity to another NNRTI should also be monitored

Hyperpigmentation

- AZT and FTC are associated with hyperpigmentation, particularly of nails, palms, and soles of darkly pigmented patients
- Stop AZT or significantly lowering the dose led to gradual resolution of the hyperpigmentation.

Bands of longitudinal hyperpigmentation of the nails of a darkly pigmented patient taking zidovudine

Hyperpigmentation of the palms in a darkly pigmented patient taking zidovudine.

ANTIRETROVIRAL-ASSOCIATED LIPODYSTROPHY SYNDROME

ANTIRETROVIRAL-ASSOCIATED LIPODYSTROPHY SYNDROME

- **Lipodystrophy** is a clinical syndrome characterized by change in body habitus attributable to fat redistribution (lipoatrophy or lipohypertrophy) and may be associated with many metabolic derangements (insulin resistance, hyperinsulinemia and a resulting hyperglycemia, and dyslipidemia)
- These symptoms may occur together or separately.
- The time course for development of lipodystrophy ranges from several months to 2 years, with changes in limb and waist circumference apparent in up to 35% of patients after 2 years of therapy

ANTIRETROVIRAL-ASSOCIATED LIPODYSTROPHY SYNDROME

- **Lipoatrophy** is defined as
  - fat loss in face (cheeks), extremities and buttocks
  - Patients often complain of prominent veins because of reduced surrounding fat
- NRTIs : d4T > AZT. May be more likely when NRTIs combined with EFV than with RTV-boosted PI
  - About 30% of patients receiving d4T for 2 years developed lipoatrophy compared with 6% of TDF.

NRTIs can cause lipoatrophy is via mitochondrial DNA (mtDNA) depletion (ddC, d4T, and ddI being the main offenders) while TDF and ABC had no effects.

Facial lipoatrophy

ANTIRETROVIRAL-ASSOCIATED LIPODYSTROPHY SYNDROME

- **lipohypertrophy** is defined as
  - visceral abdominal fat accumulation, dorsal cervical fat pad, parotid area fat accumulation, development of lipomata or enlargement of breasts (gymecomastia)
- NNTIs, Pis and INSTI : EFV, PIs and RAL

Buffalo hump

Gynecomastia in a man

Management lipodystrophy

- Switching d4T or AZT to TDF or ABC improves lipoatrophy, but normalisation can take years.
- Treatment of facial lipoatrophy by administering injectable fillers, in particular poly- L-lactic acid and calcium hydroxylapatite, which are both approved by the FDA for the treatment of HIV lipoatrophy.
- Weight loss and exercise for fat accumulation
- liposuction for dorsocervical fat accumulation and breast reduction surgery
- Metformin also improves visceral adiposity, but the effect is modest.
- Tesamorelin (growth hormone-releasing factor analog), completed phase 3 clinical trials for visceral fat reduction.
  - Results showed that patients treated for 26 weeks achieved an average 11% decrease in visceral adipose tissue (measured by Dexa scan) from baseline without significant changes in subcutaneous adipose tissue

Mitochondrial disorders

- Mitochondrial toxicity of NRTIs may contribute to many of metabolic abnormalities
  - Neuromuscular toxicities: polyneuropathy (ddC, ddI, d4T), myopathy (AZT,ddI)
  - Cardiomyopathy: AZT, ddC, ddI
  - Pancreatitis: ddI, d4T
  - Pancytopenia: AZT
  - Hepatic microvascular and macrovascular steatosis: AZT, ddI, d4T, ddC
  - Peripheral fat wasting: d4T
  - Hyperlactatemia and lactic acidosis
- Older NRTIs (d4T, ddI, AZT, ddC) are associated with a greater risk of toxicity than newer agents (3TC, FTC, ABC, TDF)

Myopathy and Cardiomyopathy

- Mitochondria DNA depletion and abnormal mitochondria have been described in skeletal and endomyocardial muscle
  - Its difficult to distinguish from caused by HIV infection per se
- Myopathy has been seen most commonly with AZT
- Myositis, increased CPK or rhabdomyolysis : RAL
- Drug-drug interaction : statin

THANK YOU