



Management of Drug Side Effects

**Modules A4 Session 3 and
Module B1 Session 4**



Objectives

1. List the common side effects of the major ARVs
2. Describe management of side effects



New Moon

FRIDAY
APRIL

8



"Now, I'm not going to tell you about the side effects because I want them to be a surprise."



Introduction

- ARVs, and drugs used to treat and prevent OIs, have some side effects. Side effects vary from person to person. Some experience few or no side effects while others have mild to severe side effects.
- Side effects often occur at drug initiation but may decrease or disappear entirely after several weeks or may persist throughout the entire time a person is taking the therapy.
- Common side effects:
 - anemia
 - headaches
 - nausea and vomiting
 - diarrhea
 - rash
 - peripheral neuropathy



Side effects: risk-benefit ratio

- Keep in mind that ALL drugs have side effects
 - Even drinking too much pure water can cause problems
 - Patients may be reluctant to discuss these
- Important concept: risk-benefit ratio
 - Every drug comes along with a risk
 - The question is whether or not the risk exceeds the benefit
 - This is part of the reason why we don't treat all patients with HIV
 - Those patients whose quality of life is already good will derive less benefit from ART, and will be less likely to be adherent and tolerant of side effects

Summary Overview of ART Adverse Effects

ARV Drug Class	Adverse Effects	
	Class-specific	ARV specific
NRTI	Mitochondrial toxicity (lactate acidosis, pancreatitis, peripheral neuropathy)	Nail pigmentation? anemia and bone marrow suppression (ZDV) Hypersensitivity (abacavir) Lipoatrophy (d4T)
NNRTI	Rash	CNS dysfunction (efavirenz) Severe hepatitis (nevirapine)
PI	Metabolic abnormalities Lipodystrophy Bleeding in hemophiliacs	Nephrolithiasis (indinavir) Diarrhea (nelfinavir, ritonavir, lopinavir) Rash (amprenavir)

Common Side Effects and Toxicities: How to Monitor

Drug Name	Side effects and Toxicity	How to Monitor
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
ZDV, AZT	<i>GI intolerance, asthenia, headache, anemia, leukopenia</i>	<i>Full blood count</i>
ddl	<i>GI intolerance: pancreatitis, peripheral neuropathy, lactic acidosis</i>	<i>Foot pain, parasthesias, deep tendon reflexes, abdominal pain</i>
d4T	<i>peripheral neuropathy, pancreatitis, lipoatrophy lactic acidosis</i>	<i>Foot pain, paresthesias, deep tendon reflexes, appearance of face</i>

Common Side Effects and Toxicities: How to Monitor, continued

Drug Name	Side effects and Toxicity (<i>toxicities italicized</i>)	How to Monitor
Nucleoside Reverse Transcriptase Inhibitors (NsRTIs)		
3TC	Generally well tolerated: <i>lactic acidosis</i>	
ABC	Hypersensitivity reaction (HSR)— symptoms of fever, rash, GI, respiratory problems; <i>lactic acidosis</i>	Educate patient on signs and symptoms of HSR and what to do; check history for prior reaction.

Common Side Effects and Toxicities:
How to Monitor, continued

Drug Name	Side effects and Toxicity (<i>toxicities italicized</i>)	How to Monitor
Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)		
TDF	<i>Uncommon: Renal impairment, decreased bone density</i>	Urea, creatinine
Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTIs)		
NVP	<i>Extensive rash, fulminant hepatitis</i>	Liver function tests q 2 wks x 2, then q mo x 12, then q 3 mo.
EFZ	<i>CNS—disassociated state x 2 to 3 weeks; Rash. Avoid pregnancy</i>	Liver function tests

Common Side Effects and Toxicities --
How to Monitor, continued

Drug Name	Side effects and Toxicity (toxicities italicized)	How to Monitor
Protease Inhibitors (PIs)		
SQV Fortovase (FTV)	<i>GI intolerance</i> , lipodystrophy	Liver function tests Lipid profile
Invirase (INV)	<i>GI intolerance</i> , paresthesias, hepatitis, lipodystrophy	Liver function tests Lipid profile
IDV	GI intolerance, <i>nephrolithiasis</i> , benign increase in bilirubin, lipodystrophy	Lipid profile Liver function tests UA

Common Side Effects and Toxicities -- How to Monitor, continued



Drug Name	Side effects and Toxicity <i>(toxicities italicized)</i>	How to Monitor
Protease Inhibitors (PIs)		
NFV	<i>Diarrhea</i> , lipodystrophy	Liver function tests Lipid profile
LPV/r	<i>GI intolerance (esp. diarrhea)</i> , asthenia, lipodystrophy	Liver function tests Lipid profile



Class Adverse Drug Reactions (ADRs)



Mitochondrial Toxicity: Lactic Acidosis ± Steatosis

- Rate: 1.3 per 1000 patient years
- Risk: Prolonged NRTI use, obesity, female sex, pregnancy, d4T > AZT, ddl > ABC, 3TC
- Symptoms: Fatigue, nausea, vomiting, wasting, abdominal pain, dyspnea, diarrhea, anorexia, weakness, myalgias, paresthesias, hepatomegaly.
- May cause respiratory failure requiring ventilator therapy.



Mitochondrial Toxicity, continued

- Other lab findings:
 - variable \uparrow CPK, LDH, lipase, amylase, ALT, anion gap
 - \downarrow HCO_3
 - CT scan or echo—fatty liver
 - liver biopsy—steatosis
- Management
 - discontinue NRTI or switch to NRTI with reduced frequency of lactic acidosis (ABC, AZT, tenofovir)
 - Supportive care



Long-term Adverse Effects of PIs

- Hepatitis
- Diabetes
- Lipodystrophy
 - ↑ cholesterol
 - ↑ triglycerides
 - Incidence increases over time on PIs



Lipodystrophy: Fat distribution

- Diagnosis
 - Fat accumulation: abdomen, dorsal neck, (“buffalo hump”), breasts
 - Fat atrophy: Extremities, buccal fat, buttocks
- Intervention
 - Results with changing therapy, including use of different classes, are inconclusive

Lipodystrophy





**Symptom-based approach to
common side effects associated with
ARVs and selected drugs for
OI Prevention and Treatment**



Anemia: possible causes

- HIV itself
- Inadequate nutrition
- Infection
- Cancers (especially leukemias)
- Side effect of medications
 - AZT, co-trimoxazole, others
- Blood loss
 - Trauma
 - Heavy menses
 - Occult or gross blood in stool



Anemia: evaluation

- History
 - Onset/duration of symptoms, medication history, diet history
- Physical
 - Particular attention to conjunctival and mucosal pallor, observe bruising/petechiae
- Laboratory
 - Hb or Hct
 - MCV
 - If feasible: reticulocyte count, vitamin levels, Parvovirus B19, peripheral smear of WBC to look for blasts
- Other suggestions?

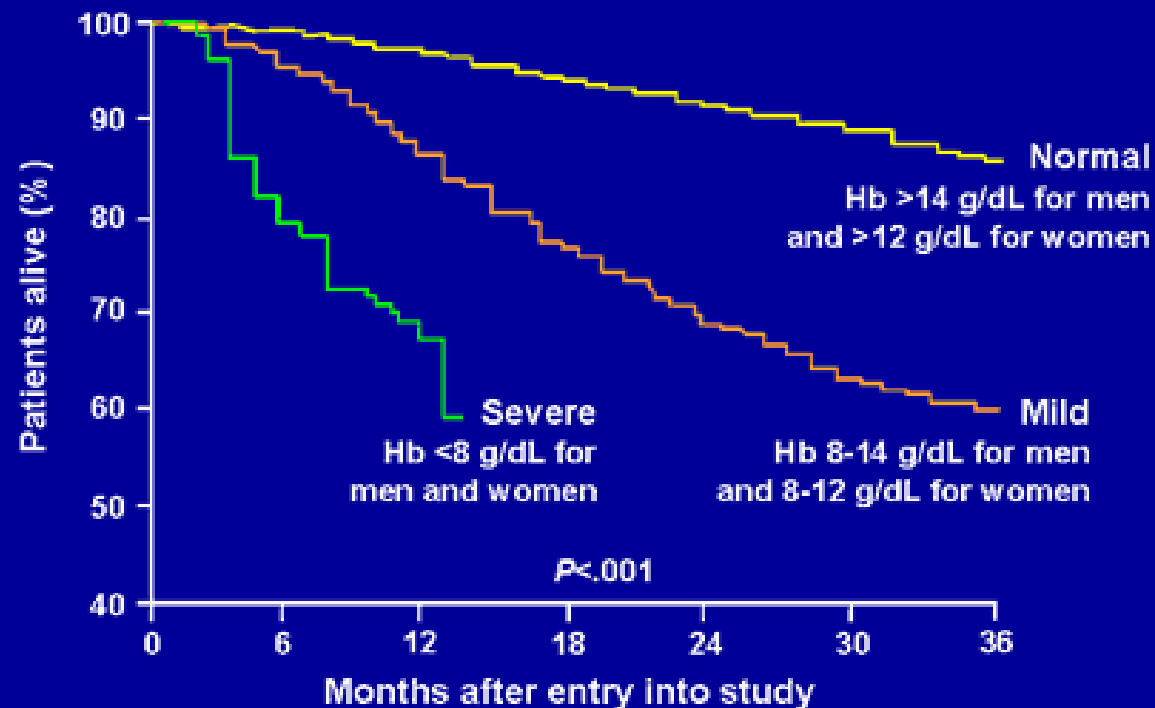


Anemia: management

- Treat cause as appropriate, if known
 - *Life threatening* anemia has been seen with AZT; however, this is easy to follow with labs and physical exam
- Change medications if necessary (i.e. substitute d4T for AZT)
- Eat diet of locally available foods high in iron, folic acid, vitamin B12 (leafy green vegetables, meat, fish, beans, etc.)
- Take multivitamins and/or supplements of iron (including injections of vitamin B12 if feasible and necessary)
- Blood transfusion if necessary

Anemia and mortality

Progression to Death for Patients According to Baseline Hemoglobin in EuroSIDA



N = 6725.

Mocroft A, et al. *AIDS*. 1999;13:943-950.



Headache: symptoms

- Ask patient to characterize headache
 - Onset, intensity, frequency, duration, location, dull/sharp, pounding, rate how bad the pain is
 - Inquire about aggravating and relieving symptoms (including relation to food or medicine ingestion, certain locations, stress)
 - Associated symptoms
 - Stiff neck, nausea/vomiting, visual disturbances, weakness, numbness, seizures, facial pain, nasal congestion/rhinorrhea, abnormal dreams
 - Others?



Headache: causes

- Stress
- Nutritional imbalances
- Exposures to irritants/chemicals
- Migraine
- Infections
 - Sinusitis, encephalitis, intracranial abscesses
 - Meningitis (including cryptococcal and TB if slow onset and/or chronic)
- Intracranial lesions
- Intracranial bleeding
- Medications
- Others?



Headache: evaluation

- THOROUGH history in characterizing headache
- Physical exam
 - Fundoscopic, look for meningismus (may be absent in cryptococcal meningitis), full neurological exam, sinus percussion/palpation
- Laboratory – guided by history and physical
 - May include LP
- Radiologic – look for intracranial lesions/bleeds, signs of increased ICP, sinusitis
- Other?

Headache - management



- Treat cause, if known
- Review medication profile
- Patient advice:
 - Headaches can generally be treated with non-prescription drugs and stress reduction
 - Avoid or limit foods or situations known to trigger headaches
 - Keep headache diary
 - Instruct patient about warning signs: visual changes, neurologic changes, headaches upon wakening, sudden onset, headaches that last more than 1-2 days
- Other?



Nausea and vomiting - symptoms

- What do you want to know in the history?
 - Frequency, duration
 - Color (is it bilious? Bloody?)
 - Associated with food intake? Drinking?
 - Able to take even sips of liquid?
 - Associated symptoms: headache, abdominal pain, diarrhea, coughing (post-tussive)
 - Anyone else have similar symptoms?
 - Medication review, including new meds and traditional meds
 - Pregnancy risk

Nausea and vomiting: possible causes



- Gastritis, gastroenteritis (including med side effect)
- Pancreatitis (including med side effect)
- Pregnancy
- Gallbladder/liver problems
- Surgical abdomen (peritonitis, ileus, etc)
- Others?



Nausea and vomiting - evaluation

- History as above
- Physical exam
 - Vital signs are VITAL
 - Check skin turgor, presence of sunken eyes, cap refill, see if mucous membranes are moist
 - Abdominal exam
 - Neuro exam especially if neuro symptoms are associated
- Laboratory
 - Electrolytes, amylase/lipase, LFTs
 - Pregnancy test
- Radiologic: HCT if indicated with neuro symptoms
- Other?



Nausea and vomiting: management

- Treat cause as appropriate, treat dehydration if present
- Anti-nausea medications
- If due to medications, consider giving with meal or light snack (except ddl) or changing meds
 - Ritonavir is especially prone to causing N/V
 - Nausea from some meds will decrease over time
- Small amounts (like sips) of liquids (ORS, water, electrolyte-replacement drinks) and increase as tolerated
- Bland, odorless foods (breads, crackers, pounded yam, porridge, potatoes, rice) in small amounts and increase as tolerated
- Avoid hot, spicy, or greasy foods, dairy foods
- Local remedies (ginger ale/beer, herbal teas, others?)



Diarrhea - symptoms

- Characterize the diarrhea
 - Frequency, consistency
 - Duration (acute/chronic)
 - Presence of blood or mucus
 - Presence of undigested food
 - Associated symptoms (abdominal pain, cramping, dry mouth, fatigue)



Diarrhea – possible causes

- Infection
 - Bacterial, viral, parasitic
 - Consider cryptosporidium, isospora, microspora if severely immunocompromised
- Malabsorption
- Medication
 - Nelfinavir is frequent culprit among ARVs
 - Antibiotics
- Others?



Diarrhea - evaluation

- History
 - Sick contacts, medication profile, characterizing the diarrhea, association with intake of certain foods
- Physical examination
 - VITAL signs
 - Check for dehydration, abdominal tenderness
- Laboratory – based on history and physical
 - Electrolytes, U/E
 - Stool examination for culture, O&P, blood, mucus, WBCs



Diarrhea - management

- Treat cause, if known
- Treat dehydration if present
- Give antidiarrheal medications, if indicated
- Antiretroviral medication and immune reconstitution may improve symptoms if caused by cryptosporidium, isospora
- A small study found that taking 500 mg of calcium twice a day greatly reduced nelfinavir-related diarrhea
- Adjust diet/intake
 - Rehydration solution
 - Rice water
 - High fiber, low fat/dairy
 - Bland foods like pounded yam, porridge, breads



Rash

- Many people get a rash when starting antiretrovirals—it is usually mild and resolves in a few weeks
- Rash is a slightly more common side effect among women taking certain antiretroviral medications.
- Nevirapine is a common cause as well as abacavir, efavirenz, amprenavir, cotrimoxazole, isoniazid, and many antibiotics.
- Women are more prone to severe rash.

- Safety of alternative NNRTIs: unknown
- Chemical structure of NNRTIs are very different and limited experience shows that a switch from NVP to EFV for rash is safe
- PI most likely to cause rash: APV—22% (sulfonamide)
- NRTI most likely to cause rash: ABC



Rash - causes

- Too many causes of rash to mention them all
- Many medications cause an initial, self-limited rash that will not require medication changes
- All rashes should be reported to clinician
- Rash could be one sign of hypersensitivity



Rash - evaluation

- Describe rash thoroughly
 - Maculopapular, desquamating, urticarial, blistering
 - Presence of pruritus
- Associated signs
 - Fever, hepatomegaly, mucous membrane involvement, difficulty breathing, wheezing
- Review client's exposures
 - Medications, plants, new soaps/lotions, sun, insect bites
- Laboratory
 - Check LFTs for nevirapine, efavirenz rashes



Rash - management

- Address cause of rash, if known
- Many rashes will respond to antihistamines, moisturizers, topical corticosteroids (except in fungal rashes)
- Avoid hot water, scented soaps and moisturizers, excessive sun exposure
- Discontinue any medications or other exposures that could be the cause
 - If blisters, fever, mucous membrane involvement, edema, arthralgias or malaise develop, discontinue ARV immediately and permanently
 - Most likely will be due to nevirapine, efavirenz, abacavir



Peripheral Neuropathy - symptoms

- Sensation of burning, stinging, stiffness, numbness, tickling in hands or feet
- Caregiver should be sure to ask about these symptoms, since a client may not think to volunteer the information
 - Should also ask client to look for these signs when starting new ARVs or anti-TB meds



Peripheral neuropathy - causes

- HIV itself
- Medications
 - INH
 - ddl
 - d4T
 - Hydroxyurea
 - Others?
- Vitamin B deficiency
- Often permanent, but may improve with appropriate management



Peripheral neuropathy - evaluation

- History
 - Initial onset (important to see if this started before any medications)
 - Frequency (constant, intermittent, daily, with exercise)
 - Intensity (affect activities of daily living?)
 - Review medication profile
- Physical exam
 - Evaluate for sensation, weakness, reflexes/clonus



Peripheral neuropathy - management

- Stop or decrease offending medication
- Multivitamin supplements
- Wear loose fitting shoes, slippers
- Massaging feet, soaking in ice water may help with symptoms
- Mild to moderate amount of walking may increase blood circulation
- Pain relief: ibuprofen, amitriptyline, L-acetyl carnitine if locally available



Summary

- All medications have side effects, patients should be informed of them
 - Most side effects can be managed without changing therapy
 - A few side effects are life threatening (but so is HIV infection)
 - Should determine if the benefits of therapy exceed the risks of side effects
- Monitoring of side effects includes following laboratory studies and asking patients about symptoms
- Clinicians should be aware of the side effects of the ARVs they prescribe to be able to detect toxicities early