

Management of Drug Side Effects

Objectives



1. List the toxicities and common side effects of each drug
2. Discuss monitoring and management of toxicities and side effects
3. Describe class adverse drug reactions, including class-specific and ARV-specific adverse effects of ART
4. Describe the important drug interactions between different ARVs and discuss the significance of these interactions

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.

Introduction, cont'd



- 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.
- When severe side effects and toxicities limit patients' ability or willingness to continue ART
 - May result in poor adherence with increased chance for development of resistant virus

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.”

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

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

Common Side Effect



- Common side effects:
 - anemia
 - headaches
 - nausea and vomiting
 - diarrhea
 - rash
 - peripheral neuropathy

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, hepatotoxicity	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 <i>(toxicities italicized)</i>	How to Monitor
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
ZDV, AZT	<i>GI intolerance, asthenia, headache, anemia, leukopenia</i>	Full blood count
ddl	<i>GI intolerance: pancreatitis, peripheral neuropathy, lactic acidosis</i>	Foot pain, amylase, lipase; deep tendon reflexes, abdominal pain, parasthesias
d4T	<i>peripheral neuropathy, pancreatitis, lipoatrophy lactic acidosis</i>	Foot pain, paresthesias, deep tendon reflexes, appearance of face; amylase, lipase

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 , FTC	Generally well tolerated: <i>lactic acidosis</i> , rash on hands (FTC)	Ask about symptoms
ABC	Hypersensitivity reaction (HSR)— symptoms of fever, rash, GI, fatigue, 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



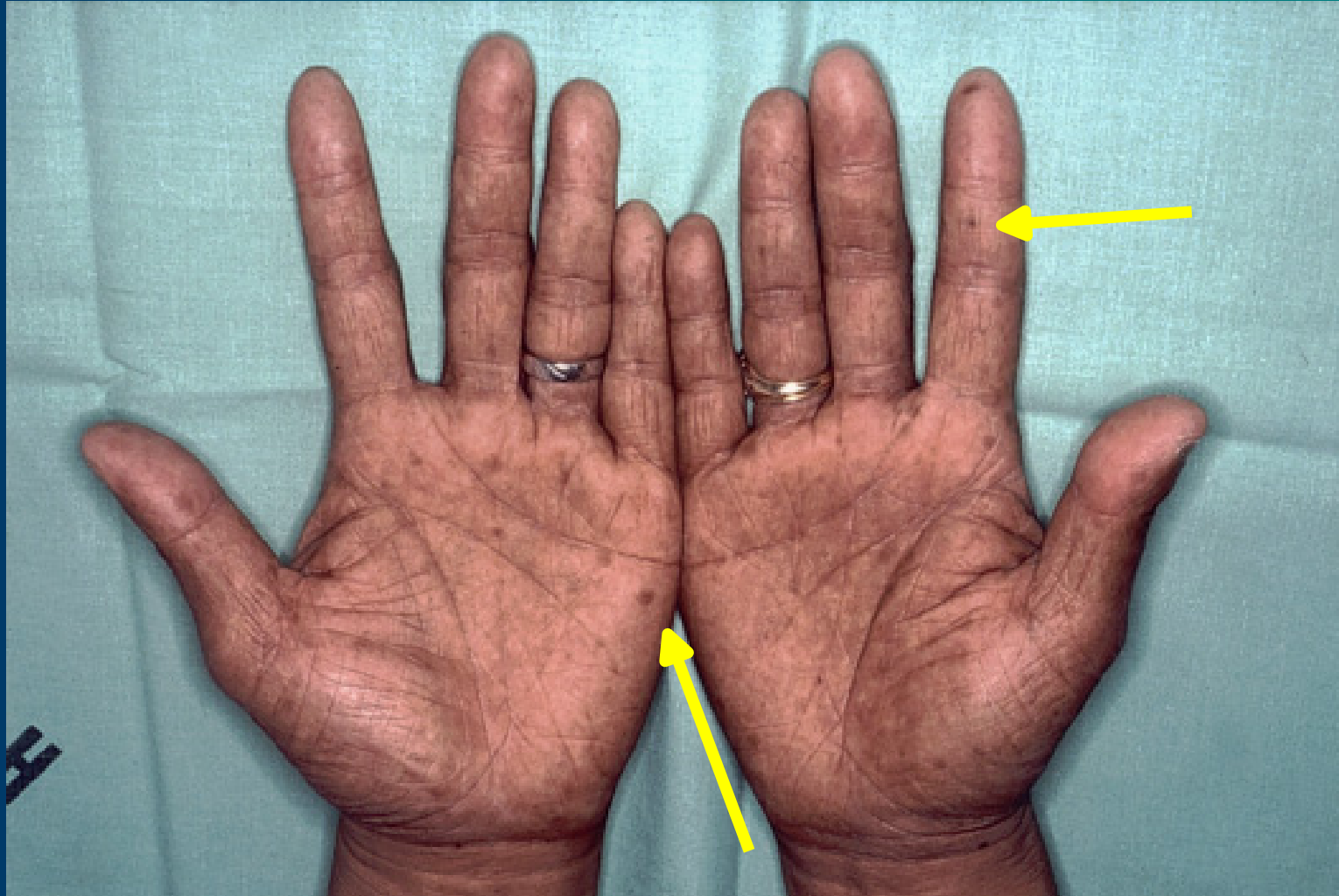
Drug Name	Side effects and Toxicity <i>(toxicities italicized)</i>	How to Monitor
Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)		
TDF	<i>Uncommon: Renal impairment, decreased bone density</i>	Urea, creatinine
Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTIs)		
NVP	<i>Extensive rash, fulminant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

Hyperpigmentation of the Palms with Emtriva



Nevirapine Hepatotoxicity



- Severe, life-threatening hepatotoxicity
 - Often associated with rash
 - Greatest risk in women with CD4 >250 (12-fold greater risk)
 - Increased risk for men with CD4 > 400 (3-fold greater risk)
 - Greatest risk during 1st 6 weeks (continued risk through 18 weeks)
 - Symptoms:
 - * often non-specific, including fatigue, malaise, anorexia, nausea, jaundice.
 - Monitoring:
 - * Transaminases at 2 weeks, 4 weeks, and regularly thereafter.
 - * Draw transaminases with any rash
 - Don't escalate NVP dose until rash resolved

Class-Related Adverse Drug Reactions (ADRs)

Mitochondrial Toxicity: Lactic Acidosis \pm Steatosis



- Rate: 1.3 per 1000 patient years
- Risk: Prolonged NRTI use, obesity, female sex, pregnancy
- d4T/ddI/Hydroxyurea > d4T/ddI > Zalcitabine > d4T > ddI > AZT, ddI > 3TC = FTC = ABC = TDF (theoretical)
- Symptoms: range from asymptomatic to severe lactic acidosis. Fatigue, nausea, vomiting, wasting, abdominal pain, dyspnea, diarrhea, anorexia, weakness, myalgias, paresthesias, hepatomegaly.
- May cause respiratory failure requiring ventilator therapy.

Mitochondrial Toxicity, continued



- Definition: Hyperlactemia = Venous lactate > 2mM

Other Lab findings:

- anion gap
- ↓ HCO₃
- CT scan or echo—fatty liver
- liver biopsy—steatosis
- Management
 - No treatment in asymptomatic hyperlactemia; observation
 - 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/insulin resistance
- Lipodystrophy
 - ↑ cholesterol
 - ↑ triglycerides
 - Incidence increases over time on PI
 - Fat accumulation primarily associated with PI
 - Fat atrophy more association with NRTI especially d4T or d4T/ddI

Lipodystrophy: Fat distribution



- Diagnosis

- Fat accumulation: abdomen, dorsal neck, (“buffalo hump”), breasts (gynecomastia), subcutaneous tissue (peripheral lipomatosis).
- Some patients show combination of Abdominal obesity + HTN + Dyslipidemia + Insulin resistance similar to Metabolic Syndrome
- Fat atrophy: loss of fat from extremities, buccal fat, buttocks

- Intervention

- Results with changing therapy, including use of different classes, are inconclusive

Lipodystrophy



Actual case



- 21 year old male with CD4 count of 5 has restarted his ARVs (previously non-adherent) during a recent hospitalization.
- He is started back on his AZT, 3TC and Kaletra
- Seven days into therapy, he complains of painful nodules in his head and neck
- He has fever to 38.8 deg C
- Otherwise feels fine, has good appetite, good spirits

What could be the problem? What would you do for him?

Slide 21

b1

Patient is suffering from immune reconstitution syndrome. He needs anti-inflammatory medications, either ibuprofen or steroids. He also needs reassurance!!!

bowman, 4/25/2006

Immune reconstitution syndrome



- For many OI, including TB, there can be a transient worsening of symptoms 2-3 or more weeks after commencing ART
- ART can unmask previously undiagnosed infections (e.g. hepatitis B or C)
- Cause is thought to be improving the inflammatory response due to the repairing of the immune system
 - Risk is higher in those with advanced HIV
- Fever, LAD, worsening pulmonary lesions
- Usually self-limiting but may require brief course of steroids AND reassurance

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 (including malaria)
- 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 (note: AZT increases MCV; d4T too but not as much)
 - * This can be used as a marker for adherence!
 - If feasible: reticulocyte count, vitamin levels, iron level, Parvovirus B19, peripheral smear of WBC to look for blasts

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
- Use of EPO (not locally widely available, costly)

Nausea/Vomiting



- Causes
 - Morning sickness, medication intolerance, gastritis, pancreatitis, hepatitis, gall bladder inflammation, increased ICP
 - * PIs often cause GI upset, ddl as well
- Evaluation
 - History, physical, U/E, amylase, lipase, LFTs, pregnancy test, HCT if neuro symptoms
- Warning signs
 - Inability to tolerate any PO, neuro symptoms, dehydration, severe abdominal pain
- Management
 - Small amts of food or liquid (sips!) and gradually increase, avoid fatty foods and dairy foods; ginger can help as can anti-nausea medications

Diarrhea



- Causes
 - Infectious, malabsorption, med side effect, others
- Evaluation
 - Characterize diarrhea, consider U/E, stool studies
- Warning signs
 - Poor urine output, dry mouth, rapid pulse (dehydration), high fever and/or severe abdominal pain
- Management
 - Treat dehydration if present
 - 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

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.

Rash



- Evaluation
 - Check LFTs for NVP and EFV rashes
- Warning signs
 - fever, hepatomegaly, mucous membrane involvement, difficulty breathing, wheezing
- 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
- Can be secondary to HIV disease or medications
 - Meds implicated: ddl, d4T, hydroxyurea, INH
- Often permanent but may improve with appropriate management

Peripheral neuropathy - management



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

Quiz:



- Which ARV is most likely to cause anaemia?
- Which ARV should be used with caution in those with a HIGH CD4 count (above 250 in women, above 400 in men)?
- Which ARV may cause abnormal dreams or cause other CNS effects?
- Which ARVs are most likely to cause peripheral neuropathy?

- Which ARV is most likely to cause anaemia?
AZT
- Which ARV should be used with caution in those with a HIGH CD4 count (above 250 in women, above 400 in men)?
NVP
- Which ARV may cause abnormal dreams or cause other CNS effects?
EFV
- Which ARVs are most likely to cause peripheral neuropathy?
d4T, ddI

Quiz



- Which class of ARVs is most likely to cause lipodystrophy and metabolic abnormalities?
- Which ARV may cause hypersensitivity reaction with symptoms such as fever, rash, GI symptoms, hypotension and rash?
- Which ARV is used only once a day for first 2 weeks and whose dose is changed to twice a day if there's no rash or hepatotoxicity?
- Which ARV is most likely to cause an increase in MCV, which can be used as a marker for adherence?

- Which class of ARVs is most likely to cause lipodystrophy and metabolic abnormalities?

Protease inhibitors

- Which ARV may cause hypersensitivity reaction with symptoms such as fever, rash, GI symptoms, hypotension and rash?

Abacavir

- Which ARV is used only once a day for first 2 weeks and whose dose is changed to twice a day if there's no rash or hepatotoxicity?

Nevirapine

- Which ARV is most likely to cause an increase in MCV, which can be used as a marker for adherence?

AZT

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