Complications of Antiretroviral Therapy
Management of ART Toxicity

• Mild adverse effects
  – Continue therapy
  – Patient education; reassurance

• Severe or intolerable adverse effects
  – Single-drug substitution, same class
  – Simultaneous discontinuation of all drugs
  – Staggered discontinuation
    • First NNRTIs
    • NRTIs 5–7 days later
Common Toxicities of NRTIs

- Mitochondrial toxicity (all; esp. stavudine)
  - Lipoatrophy
  - Hepatic steatosis; lactic acidosis
  - Peripheral neuropathy
- Bone marrow suppression (zidovudine)
- Myopathy, myositis (zidovudine)
- Pancreatitis (didanosine)
- Renal impairment (tenofovir)
- Hypersensitivity reaction (abacavir)
Common Toxicities of PIs

- Fat accumulation (all agents)
- Dyslipidemia (all)
- Hepatotoxicity (all)
- Hyperglycemia (all)
- Increased bleeding in hemophilia (all)
- Osteopenia/osteoporosis (all)
- ECG changes (atazanavir)
- Hyperbilirubinemia (atazanavir, indinavir)
- Nephrolithiasis/urolithiasis (indinavir)
- Skin changes (indinavir)
Severe Hepatotoxicity by ART Regimen

Overall Groups

- Overall
- NRTIs
- PIs

PI Subgroups

- RTV
- RTV/SQV
- SQV
- IDV
- NFV

P-mo = person-months.
Common Toxicities of NNRTIs

• Rash (all agents)
  – May include severe morbidity and mortality
• CNS effects (efavirenz)
• Teratogenicity (efavirenz)
  – Pregnancy category D; neural tube defects
• Hepatotoxicity (all; especially nevirapine)
  – Use nevirapine cautiously
  – Adequate CD4 counts; monitor liver function
Common Toxicities of Fusion Inhibitor

Enfuvirtide is the only approved agent
• No known systemic toxicity
• Injection-site reactions in nearly 100%
  – Redness
  – Itching
  – Swelling
  – Pain
  – Hard skin or lumps
Long-term Complications of ART: Fat Maldistribution Syndromes

- Lipoatrophy
  - Most common morphologic abnormality
  - Due to mitochondrial toxicity of NRTIs

- Fat accumulation
  - Less common than lipoatrophy
  - Thought to be due to PI therapy
Changes in Body Fat Indices with ART

Lipoatrophy by ART Regimen: Changes at 144 Weeks

Lipoatrophy by ART Regimen: NRTIs vs NRTI-Sparing Regimen

% with Lipoatrophy

Week 48
- EFV+NRTIs
- LPV/r+NRTIs
- LPV/r+EFV

Week 96
- EFV+NRTIs
- LPV/r+NRTIs
- LPV/r+EFV

Lipoatrophy by ART Regimen: Effect of Switching Stavudine

Mitochondrial Toxicity by ART Regimen: Effect of Switching Stavudine

mtDNA Copies per Cell Type

- Muscle
- Fat
- PBMCs

Apoptosis Score

Wk 0   Wk 48   HIV−

Long-term Complications of ART: Lipid Effects

Lipid effects include elevated TC, LDL-C, TGs

• PIs
  – Highest risk among ART classes
  – Especially ritonavir

• NRTIs
  – Highest risk with stavudine, then zidovudine

• NNRTIs
  – Highest risk with nevirapine and efavirenz
  – But also improvement in HDL-C
Dyslipidemia Due to HIV and ART

## Lipid Effects of PIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>TG / VLDL-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>↑↑↑↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Lopinavir / ritonavir</td>
<td>↑↑</td>
<td>↑</td>
<td>↔/↑</td>
</tr>
<tr>
<td>Tipranavir / ritonavir</td>
<td>↑↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Saquinavir / ritonavir</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Fosamprenavir / ritonavir</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Indinavir / ritonavir</td>
<td>↑↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Darunavir / ritonavir</td>
<td>↑</td>
<td>↑/↔</td>
<td>↑?</td>
</tr>
<tr>
<td>Atazanavir / ritonavir</td>
<td>↑</td>
<td>↑/↔</td>
<td>↑</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>↔/?</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>↔</td>
<td>↔</td>
<td>↔/↑?</td>
</tr>
<tr>
<td>Indinavir</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
</tr>
</tbody>
</table>
Management of Dyslipidemia

Apply NCEP guidelines

- Lifestyle changes
- Lifestyle + lipid-lowering therapy (statin)
- ART substitution
- Consider fibrates for TGs

Challenges of lipid-lowering therapy

- Multiple medications
- Drug–drug interactions (statins, PIs)
- Difficulty reaching NCEP goals despite therapy
Lipid-Lowering Therapy: Drug–Drug Interactions with ART

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Lipid-lowering Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low potential for interaction</td>
<td>Fibrates</td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin</td>
</tr>
<tr>
<td></td>
<td>Fish oil</td>
</tr>
<tr>
<td></td>
<td>Niacin*</td>
</tr>
<tr>
<td>Start lowest dose; use cautiously</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin</td>
</tr>
<tr>
<td>Contraindicated with PIs</td>
<td>Lovastatin</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
</tr>
</tbody>
</table>

* In rare cases, can induce insulin resistance.
Long-term Complications of ART: Insulin Resistance and Diabetes

• Risk factors
  – Reduction in insulin sensitivity with PIs
  – Long-term exposure to NRTIs
  – HCV coinfection; traditional risk factors

• Management
  – Fasting glucose level before ART
  – Routine glucose monitoring; possible GTT
  – IGT or diabetes: consider switch to NNRTIs
## Insulin Resistance by ART Regimen

<table>
<thead>
<tr>
<th>Group (per 1-yr increase in ART)</th>
<th>Difference in QUICKI</th>
<th>OR, insulin &gt;15 μU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>−0.27 (−0.49 to −0.05)*</td>
<td>1.59 (1.07–2.35)*</td>
</tr>
<tr>
<td>PI</td>
<td>0.00 (−0.04 to 0.04)</td>
<td>1.06 (0.99–1.14)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>−0.05 (−0.12 to 0.02)</td>
<td>1.14 (1.02–1.26)*</td>
</tr>
<tr>
<td>NNRTI</td>
<td>0.01 (−0.05 to 0.07)</td>
<td>0.95 (0.84–1.06)</td>
</tr>
<tr>
<td>NRTI</td>
<td>−0.04 (−0.07 to −0.01)*</td>
<td>1.08 (1.02–1.13)*</td>
</tr>
<tr>
<td>Stavudine</td>
<td>−0.11 (−0.17 to −0.05)*</td>
<td>1.22 (1.11–1.35)*</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>−0.06 (−0.12 to 0.00)*</td>
<td>1.12 (1.02–1.24)*</td>
</tr>
</tbody>
</table>

QUICKI = quantitative insulin sensitivity check index; OR = odds ratio.
* $P < 0.05$.
# Diabetes by ART Regimen

![Bar chart showing prevalence of diabetes by ART regimen](chart.png)

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence *</th>
<th>Incidence †</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV‒</td>
<td>1</td>
<td>1.4 (0.8–2.6)</td>
<td>1</td>
</tr>
<tr>
<td>HIV+, no Tx</td>
<td>2.21 (1.12–4.38)</td>
<td>1.7 (0.6–4.5)</td>
<td>NA</td>
</tr>
<tr>
<td>HIV+, HAART</td>
<td>4.64 (3.03–7.10)</td>
<td>4.7 (3.2–7.1)</td>
<td>4.11 (1.85–9.16)</td>
</tr>
</tbody>
</table>

RR = rate ratio adjusted for age and body mass index; NA = not applicable.

* Prevalence ratio based on 1278 men; adjusted for age and body mass index.
† Incidence rate per 100 person-years, based on 680 men.

Long-term Complications of ART: Cardiovascular Risk

- Risk factors
  - Dyslipidemia
  - Insulin resistance
  - Lipodystrophy
  - Endothelial dysfunction
  - Smoking
  - Duration of ART
  - PIs seem to be mainly responsible

- Management: continue therapy
**Myocardial Infarction by ART Regimen**

**Graph:**
- Y-axis: MI Incidence per 1000 p-yr
- X-axis: Years of Exposure to ART
- The graph shows an increasing trend in MI incidence with longer years of exposure to ART.

**Table:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ART</td>
<td>1.16</td>
<td>1.09–1.23</td>
</tr>
<tr>
<td>PIs</td>
<td>1.16</td>
<td>1.10–1.23</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>1.05</td>
<td>0.98–1.13</td>
</tr>
</tbody>
</table>

p-yr = person-years; RR = relative rate per year of exposure.
Long-term Complications of ART: Lactic Acidosis

• Asymptomatic hyperlactatemia
  – Mildly elevated blood lactate
  – Does not predict lactic acidosis
• Symptomatic hyperlactatemia
  – Nonspecific symptoms
• Lactic acidosis syndrome
  – Severe symptomatic hyperlactatemia
  – Metabolic acidosis, hepatomegaly, steatosis
  – Rare but often fatal
  – Stop NRTI treatment
Hyperlactatemia by ART Regimen

* $P = 0.03$.
## Hyperlactatatemia Risk Factors

<table>
<thead>
<tr>
<th>Significant Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (per 10 U/L) *</td>
<td>1.13</td>
<td>1.001–1.3</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>NRTI treatment</strong> *</td>
<td>3.0</td>
<td>1.0–9.27</td>
<td>0.05</td>
</tr>
<tr>
<td>Stavudine (n = 56) †</td>
<td>2.8</td>
<td>1.4–5.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Stavudine/lamivudine (n = 40) †</td>
<td>2.2</td>
<td>1.0–4.8</td>
<td>0.05</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; ALT = alanine aminotransferase.

* Multiple logistic regression analysis.
† Unadjusted univariate analysis.

Long-term Complications of ART: Distal Sensory Peripheral Neuropathy

• Characteristics
  – HIV-related causes
  – NRTIs (esp. stavudine + didanosine)
  – Risk is higher with advanced HIV
  – Pain, numbness, loss of sensation

• Management
  – Discontinue NRTIs
  – Adjunctive treatments for persistent pain
## Peripheral Neuropathy by ART Regimen

![Bar chart showing incidence of peripheral neuropathy by ART regimen](chart.png)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T</td>
<td>1.39</td>
<td>0.84‒2.32</td>
<td>0.20</td>
</tr>
<tr>
<td>ddl+HU</td>
<td>2.35</td>
<td>0.69‒8.07</td>
<td>0.18</td>
</tr>
<tr>
<td>ddl+d4T</td>
<td>3.50</td>
<td>1.81‒6.77</td>
<td>0.001</td>
</tr>
<tr>
<td>ddl+d4T+HU</td>
<td>7.80</td>
<td>3.92‒15.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

HU = hydroxyurea; HR = hazard ratio.
Adapted from Moore RD, et al. AIDS. 2000;14:273-278.
Summary: Common Adverse Effects

**NRTIs**
- Mitochondrial toxicity
- Lipoatrophy
- Hepatic steatosis
- Lactic acidosis
- Peripheral neuropathy
- Bone marrow suppression
- Myopathy
- Pancreatitis
- Renal impairment
- Hypersensitivity

**PIs**
- Lipodystrophy
- Dyslipidemia
- Hepatotoxicity
- Hyperglycemia
- Hemophilia bleeding
- Osteoporosis
- ECG changes
- Hyperbilirubinemia
- Urologic stones
- Skin changes

**NNRTIs**
- Rash
- CNS effects
- Teratogenicity
- Hepatotoxicity

**Fusion inhibitor (enfuvirtide)**
- Injection-site reactions
Summary:
Management of Adverse Effects

• Adjunctive strategies:
  – Choose agents carefully
  – Optimize lifestyle

• Pharmacologic strategies:
  – Mild effects: continue therapy
  – Moderate effects: single-drug substitution
  – Severe effects: discontinuation