Mitochondrial Toxicity in Antiretroviral Therapy

Andrew Stolbach
Case

- A 25-year-old man from Malawi presents with abdominal pain, fatigue, and weight loss of several weeks duration

- Past medical history includes HIV

- On examination, vital signs are normal, abdomen is mildly tender without peritoneal signs

- Laboratory studies indicate lactate of 4.4 mmol/L
Baltimore
Johns Hopkins Hospital
35,000,000 Adults and Children living with HIV
<table>
<thead>
<tr>
<th>Metropolitan Area</th>
<th># of Cases</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miami, FL</td>
<td>49,045</td>
<td>879.3</td>
</tr>
<tr>
<td>New York</td>
<td>143,393</td>
<td>757.9</td>
</tr>
<tr>
<td>Baltimore</td>
<td>18,318</td>
<td>674.8</td>
</tr>
</tbody>
</table>

ART Reduces Viral Load Below the Limit of Detection

Homayoon Farzadegan, Johns Hopkins University
Deaths Dropped Abruptly Following Institution of ART

AIDS Diagnoses and Deaths of Adults and Adolescents with AIDS, 1985–2009—United States and 6 U.S. Dependent Areas

Note: All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting. Deaths of persons with an AIDS diagnosis may be due to any cause.

Richard Moore, Johns Hopkins University
### Recommended Initial Antiretroviral Regimens

<table>
<thead>
<tr>
<th>Type of Regimen</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrase inhibitor plus 2 NRTIs</td>
<td>Dolutegravir plus tenofovir/emtricitabine</td>
</tr>
<tr>
<td>NNRTI plus 2 NRTIs</td>
<td>Efavirenz/tenofovir/emtricitabine</td>
</tr>
<tr>
<td>Protease Inhibitor plus 2 NRTIs</td>
<td>Atazanavir plus tenofovir/emtricitabine</td>
</tr>
</tbody>
</table>

2014 Recommendations of the International Antiviral Society–USA Panel
Reverse Transcriptase

- Creates DNA from viral RNA
- Reverse transcriptase is a DNA polymerase!
Mitochondrial Toxicity

1. NRTI inhibition of mtDNA Polymerase
2. Depletion of mtDNA
3. Disruption of production of mitochondrial protein
4. Failure of mitochondria
<table>
<thead>
<tr>
<th>NRTI</th>
<th>Potential for mitochondrial toxicity</th>
<th>Other predominant toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>+</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>Didanosine (dDI)</td>
<td>+++++</td>
<td>Pancreatitis, peripheral neuropathy</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>+</td>
<td>Mild headache, rash, GI upset</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>+</td>
<td>Constitutional symptoms</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>+++++</td>
<td>Lipoatrophy, pancreatitis, peripheral neuropathy</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>+</td>
<td>Fanconi’s syndrome, renal insufficiency, gastrointestinal upset</td>
</tr>
<tr>
<td>Zalcitabine (no longer availabe)</td>
<td>+++++</td>
<td>Thrombocytopenia (5 %), anemia (10 %), pancreatitis, cardiomyopathy, peripheral neuropathy (35 %), lactic acidosis</td>
</tr>
<tr>
<td>Zidovudine (ZDV, AZT)</td>
<td>++</td>
<td>Myelosuppression, lipodystrophy</td>
</tr>
</tbody>
</table>

Margolis et al 2013
Manifestations of Mitochondrial Toxicity

Lipoatrophy  Myopathy  Neuropathy  Lactic acidosis
Manifestations of Mitochondrial Toxicity- Lipoatrophy

Asymmetric loss of body fat from face and extremities
Manifestations of Mitochondrial Toxicity- Myopathy

- NRTI inhibition of muscle mtDNA polymerase
- Zidovudine
Manifestations of Mitochondrial Toxicity - Neuropathy

- Neuropathy associated with HIV and treatment of HIV
- Laboratory evidence supports role of NRTI and mtDNA
Manifestations of Mitochondrial Toxicity- Hepatic Steatosis

- Decreased mitochondrial beta $\beta$-oxidation of fatty acids
- Esterification of triglycerides
- Triglycerides accumulate in the liver
Manifestations of Mitochondrial Toxicity - Lactic Acidosis

- Insufficient oxidative phosphorylation
- Pyruvate is metabolized to lactate (rather than acetyl CoA)
- Hepatic dysfunction may be a prerequisite
Clinical Manifestations of NRTI Hyperlactatatemia

- Malaise
- Dyspnea
- Abdominal pain
- Nausea/vomiting
- Weight loss
Incidence

- Mild (median lactate 4.4 mmol/L):
  - 20.9 cases in 1,000 patient-years

- Moderate (mean lactate 5 mmol/L) with Steatosis
  - 3.9 cases in 1,000 patient-years

- Severe (mean lactate 6.5 mmol/L, ph<7.4)
  - 0.85 cases per 1,000 patient years

Algorithm for the management of elevated plasma lactates

Lactate
- L < 2 mmol/L (Watchful waiting)
- 2 < L < 5
  - Symptomatic??
    - No
      - Stop NRTIs
    - Yes
      - Repeat measurement (standardize conditions)
- L > 5 mmol/L
  - L > 5 mmol/L acidosis?
    - Yes
      - Add vitamins
    - No
A 25-year-old emigrant from Malawi presents with abdominal pain, fatigue, and weight loss of several weeks duration.

Past medical history includes HIV.

On examination, vital signs are normal, abdomen is mildly tender without peritoneal signs.

Laboratory studies indicate lactate of 4.4 mmol/L.
Case

- Further history indicates he is on stavudine
- Discuss case with his primary care doctor
- Change him to a different NRTI or NRTI-free regimen
Conclusions

More people living with HIV

Consider mitochondrial toxicity in HIV patients with neuropathy or myopathy

Hyperlactatemia may present with vague symptoms

Change affected patients to newer NRTIs or non-NRTI regimens