Lactic Acidosis and Ascending Neuromuscular Syndrome

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Introduction

- ART is rapidly scaling up in resource poor countries
- The primary combination in many countries is d4T/3TC and Nevirapine
  - Inexpensive
  - Available as a Fixed dose combination
Introduction

• Potential toxicity related to long term use of this combination is Lactic Acidosis (LA)
• Stavudine commonly causes peripheral neuropathy
• Lactic Acidosis can be associated with an Ascending neuromuscular Syndrome
Risk Factors for Lactic Acidosis

- Female Sex
- D4T/DDI > D4T > DDI = ZDV > 3TC = Abacavir (ABC)
  - Not yet seen in Tenofovir (TDF)
- Duration of therapy
- Pregnancy
- Pre-existing Liver Disease
- Obesity
Background

- FDA reported in 2002
- 25 cases of Lactic Acidosis cases with Neuromuscular toxicity (CROI, 2002 LB-14)
  - 7 deaths
  - 22 were on stavudine-containing regimens
  - 8 pregnant women
• FDA case definition of “Ascending Neuromuscular Weakness syndrome”
  - Neuromuscular weakness
  - Lactic acidosis or symptomatic hyperlactatemia
  - Events occurred with 4-5 weeks of each other
Case 1

- 35 yo Male started on D4T/DDI/Nelfinavir in July 2001
  - CD4=47
  - WHO Stage 3- PTB
- CD4 increased to 241 in 6 months but never undetectable
• September 11, 2002, he presented with one week of severe pain in the feet with mild edema
  – CD4 dropped to 197
• ART discontinued for Neuropathy and Failure
• Neuropathic pain increased and he developed progressive weakness of both upper and lower extremities.
• October 1\textsuperscript{st}, 2/5 lower extremity strength and 3/5 upper extremity strength and was bedbound.

• Abdominal distension, nausea and lost 10 kg
  - Available work-up limited (no capability for lactate)

• CLINICAL DIAGNOSIS of lactic acidosis with ascending motor paralysis was made
• 10/2002: Started on Nevirapine/Kaletra due to rapidly declining CD4 off ART (102).

• Gradual improvement in muscle strength over the next year.

• Able to walk with a cane by one year

• Current status
  - Ambulatory with normal strength except mild foot drop of left foot.
  - CD4=393, HIVRNA<400 copies
Case 2

- 43 yo male started Triomune Jan 21 2003 with CD4=7, WHO stage IV (Cryptococcal Meningitis)
- Follow-up CD4=72, HIVRNA<50, Weight gain of 15kg
Case 2, cont

- August 2005- 9 kg weight loss noted, CD4 ordered for possible failure
  - CD4 = 203, No FAILURE
  - ? Early lactic acidosis

- Sept 16, 2005- Vomiting, reflux, reduced appetite, Another 1.5 kg Weight loss
  - Abdominal Ultrasound- Normal
  - Cardiac Ultrasound- Normal
Case 2, cont

- Oct 13th, 2005- New onset Neuropathy
  - Amitriptyline
- Oct 18th 2005- Worsening Neuropathy
  - able to walk
  - Pyridoxine
- Oct 24th 2005- Worsening Neuropathy
  - Weakness, decreased ability to walk
  - Pyridoxine, ART refilled
Case 2, cont

- Oct 28\textsuperscript{th} 2005- Worsening Neuropathy-
Marked muscle weakness and shortness of breath
  - Pyridoxine
- Oct 31\textsuperscript{st} 2005- Unable to walk (3/5 leg strength, 4/5 Upper extremity weakness, Marked dyspnea (50-60 RR)
Case 2, cont

- Lactate = 9.3 mmol/L
- CO2 = 7
- Anion Gap = 23

ART stopped
IV hydration given
Prayer
Case 2, cont

- **December 2005**
  - Lactate returned to Normal = 2.5 mmol
  - Able to walk with cane

- **January 2006**: Started on NVP/Kaletra

- **June 2006**: HIV RNA < 400 copies
  - Able to walk unaided
Case 3

• 39 yo male started Triomune April 14, 2004 with CD4 19, WHO stage III
• Gained 18kg, CD4 increased to 203 by December 2004.
Case 3, cont

- March 20, 2005
  - Presented with vomiting x 1 week, 14kg weight loss, muscle pain of entire body, and abdominal distension.
  - Lactate= 7.2
  - ART immediately discontinued
Case 3, cont

• April 6, 2005
  - Worsening muscle weakness
  - Lactate increased to 8.3

• April 13th 2005
  - Unable to walk secondary to muscle weakness
    (4/5 quad strength, 3/5 Ankle dorsiflexion)

• May 4th 2005
  - Weakness stabilized (Unable to walk)
  - Lactate= 3.1

• August 2005
  - Able to walk with cane
Lactic Acidosis in Malawi

• Retrospective review of the files of all patients in which a lactate was performed at UNC Project-Lilongwe and a diagnosis of Lactic Acidosis was made
  - Referrals from inpatient wards
  - Referrals from private clinics
  - Referrals from Lighthouse HIV clinic
Clinical findings at our setting

- 20 cases Lactic Acidosis identified
  - 65% Female
  - Mean age 40.4
  - 100% were on Stavudine
  - Duration on ART at time of Lactic Acidosis
    602 days (286-1358)
  - Mean increase in CD4 on ART- 173 cells
<table>
<thead>
<tr>
<th>Clinical Findings at our site</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathy</strong></td>
<td>90%</td>
</tr>
<tr>
<td><strong>Muscular Weakness</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>40%</td>
</tr>
<tr>
<td>Mild</td>
<td>35%</td>
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<tr>
<td>Severe</td>
<td>25%</td>
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<tr>
<td>Cardiac</td>
<td>30%</td>
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<tr>
<td>Respiratory (SOB, dry cough)</td>
<td>35%</td>
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<tr>
<td>Gastrointestinal</td>
<td>90%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>84%</td>
</tr>
<tr>
<td>Mean loss 9.6kg</td>
<td></td>
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</tbody>
</table>
Lab Findings

- Mean Lactate= 7.4  Range (3.5-14.8)
- Increased LFTs-
  - 42 % with Grade 1 abnormalities
  - Others were not done
Our Results

- 3 Deaths (Lactate over 10)
- 1 TDF/3TC/Kaletra
- 5 patients tolerated AZT/3TC/NVP
- 4 Patients NVP/Kaletra
- 7 Pending treatment
Lilongwe conclusions

• High proportion of neurologic and muscular findings in lactic acidosis cases
  – Follows cessation of ART

• Mortality associated with highest lactates
Limitations

- Retrospective
- Only confirmed LA cases
- Excludes those where LA was not diagnosed
- High muscle weakness may be due to ability to identify its association with LA
- No ability to characterize EMG, nerve conduction or biopsy
Background

- Retrospective identification of potential cases
- HIV infected
- New Onset Limb Weakness of neuromuscular cause (with/without sensory change)
  - Either lower limbs
  - Both lower and upper limbs
- Acute (1-2 weeks) or Subacute (>2 weeks)

Simpson, et al. AIDS, 2004: 18 (10); 1403-1412
- 69 cases of neuromuscular weakness identified
  (27 definite, 19 probable, 23 possible)
- 63% had hyperlactatemia (>2.2mmol/L)
- 68/69 were on ART including NRTI
- 61/69 (89%) were on Stavudine
Definite cases

- Nerve conduction and EMG were done in 24 subjects
  - 20 sensorimotor polyneuropathy
    - 13 Axonal
    - 2 Demyelinating
    - 4 Mixed
    - 1 Unidentified
Definite Cases

• Muscle Biopsy in 15 patients
  - 3 Generalized myofiber atrophy
  - 3 Inflammatory infiltrates
  - 4 “Mitochondrial dysfunction”
    • Ragged Red fibers
    • DNA depletion
    • Abnormal respiratory chain enzymes
Outcomes

- 9 Deaths (associated with lactate level)
- 16 required intubation
- 19 had residual neurological deficits
Summary

- Lactic Acidosis is a potentially fatal condition that requires cessation of ART.
- Progressive neurologic dysfunction can persist and worsen after cessation of ART when associated with Lactic acidosis.
- Rapid onset neuropathy with/without muscle weakness may indicate lactic acidosis.
- The ascending neuromuscular syndrome may be due to Mitrochondrial toxicity.
Future

- Better characterization of the rate of this syndrome is required as the population at risk is great and increasing
- Standardized, clinical assessments and evaluation among prospectively identified cases is required.