ARV related toxicities

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

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WHO Training Course for Introducing Pharmacovigilance of HIV Medicines

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Acknowledgements

sources of slide material

Published data
Jens Lundgren
WHO – draft clinical management guidelines
SA – clinical management guidelines
DART study group
Targets for Antiretroviral Drugs in HIV Life Cycle

Reeves & Piefer, 2005
### ARV drugs in the “Public Health Approach”

<table>
<thead>
<tr>
<th>NRTI</th>
<th></th>
<th>Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT / ZDV)</td>
<td></td>
<td>Saquinavir</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td></td>
<td>Indinavir</td>
</tr>
<tr>
<td>Stavudive (d4T)</td>
<td></td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td></td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td></td>
<td>Lopinar + Ritonavir</td>
</tr>
<tr>
<td>Tenofovir DF (TDF)</td>
<td></td>
<td>Atazanavir *</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td></td>
<td>Darunavir *</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
<td><strong>Integrase Inhibitor</strong></td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>Raltegravir *</td>
</tr>
<tr>
<td>Efavirenz</td>
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</tbody>
</table>

* Revised Guidelines
ARV Toxicities

description

Occurrence
- How frequent
- In whom

Clinical Recognition
- Signs & symptoms
- Laboratory features
- Severity grading

Management
- Specific Treatment
- Adjustment in ART
- Prevention
- Safety monitoring

categorisation

Class specific or Drug specific

Affected Organ System
- Database reports

Clinical significance
- Minor / Transient
- Life threatening
- Treatment limiting
- Effect on adherence
NRTI Class Related Toxicity

1. NRTIS CLASS SPECIFIC TOXICITY - MITOCHONDRIAL TOXICITY (FAT ATROPHY, LACTIC ACIDOSIS, PANCREATITIS, CARDIOMYOPATHY)

2. ZIDOVUDINE
3. TENOFOVIR
4. ABACAVIR
NRTIs – Mitochondrial toxicity

Energy powerhouses of cell & possess own DNA

NRTIs inhibit *mtDNA polymerase gamma*

Decreased *mtDNA* synthesis

Dysfunctional mitochondria

Insufficient amounts of ATP

Tissue and Organ dysfunction

Increased lactate levels
NRTIs: hierarchy of *in vitro* inhibition of mtDNA

Zalcitabine
Didanosine
Stavudine
Zidovudine
Lamivudine
Abacavir
Tenofovir

*FIGURE 1. Mitochondrial toxicity in human cells. Adapted with permission. SkMC, skeletal muscle cells; ZDV, zidovudine; 3TC, lamivudine; ABC, abacavir.*
Clinical manifestations of mitochondrial toxicity associated with different NRTIs

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlactatemia / Lactic Acidosis</td>
<td>d4T &gt; ddI &gt; ZDV &gt; other NRTIs</td>
</tr>
<tr>
<td>Lipoatrophy / Lipohypertrophy (LYPODYSTROPHY)</td>
<td>d4T &gt; ZDV &gt; other NRTIs</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>ddC &gt; d4T &gt; ddI</td>
</tr>
<tr>
<td>HIV-associated neuromuscular weakness</td>
<td>?d4T &gt; other NRTIs</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>ddI &gt; other NRTIs</td>
</tr>
<tr>
<td>Hepatic Steatosis</td>
<td>D4T &gt; ddI</td>
</tr>
<tr>
<td>Skeletal Myopathy / Cardiomyopathy</td>
<td>ZDV</td>
</tr>
<tr>
<td>Adverse effects on maternal / fetal health</td>
<td>d4T + ddI</td>
</tr>
</tbody>
</table>
Lipoatrophy: Model for Disease Pathogenesis

Risk Factors

- Genetic
- Environmental
- HIV-related
- ART-related

Pathogenic mechanism

- May be quantified by specific diagnostic techniques

Subclinical disease

- Clinically apparent, overt pathology

Clinical event

- Clinical fat wasting

Time

10-40 months
# Lactic Acidosis

- **Rare but potentially life threatening**
  - Case fatality of LA is up to 60%

## Risk Factors
- Older age (unusual in young children)
- Female gender
- High body mass index
- Pregnancy
- Underlying liver disease

## Clinical Recognition
- **Symptoms**: high index of suspicion
- **Lab**: ↑serum lactate + Acidosis
  - Measure: Serum lactate/HCO₃ /Na+/K+
  - then calculate the anion gap
  - Measure: Serum Lactate / HCO₃/Blood pH

## Management
- Discontinue ART for at least 4 weeks (till lactate levels normalise)
- Hospital treatment according to severity
- Substitute TDF or ABC for d4T,ddl or ZDV
- Avoid all future use of d4T / ddl

## Safety Monitoring
- Clinical suspicion — esp. high risk profiles
- Lactate measurements not recommended
# Pancreatitis

## Risk Factors
- Past pancreatitis
- Alcoholism
- ↑ Tryglycerides
- CD4 count < 50 cells/mm³

Most commonly associated with ddI

## Clinical Recognition
- Typical clinical symptoms & signs
- Lab: Raised Serum Amylase
- Imaging: Abdominal Ultrasound / CT scan

## Management
- Discontinuation of ART
- Hospitalisation often required
- Management of risk factors
- Avoid ddI + d4T/TDF/Ribavirin

## Safety monitoring
- Symptom driven investigation
- Routine monitoring of serum amylase is not recommended
## Cardiomyopathy

<table>
<thead>
<tr>
<th>Rare: most often related to Zidovudine</th>
<th>Clinical Recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>Syndrome of congestive heart failure</td>
</tr>
<tr>
<td>Other viral infections</td>
<td></td>
</tr>
<tr>
<td>Substance abuse: Alcohol / Cocaine/DxA</td>
<td></td>
</tr>
<tr>
<td>Severe Anaemia / Thyrotoxicosis</td>
<td></td>
</tr>
<tr>
<td>Thiamine / Zinc deficiency</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management</th>
<th>Safety Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion of other causes</td>
<td>Clinical symptom driven investigation</td>
</tr>
<tr>
<td>Treatment of heart failure</td>
<td></td>
</tr>
<tr>
<td>Substitution of ZDV</td>
<td></td>
</tr>
</tbody>
</table>
Some programme experience

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Frequency of ARV substitution for toxicity (period on ART)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>neuropathy, lipoatrophy, pancreatitis, lactic acidosis</td>
<td>24 % (22 months)</td>
<td>AIDSRelief (Kenya, Uganda, Tanzania)</td>
</tr>
<tr>
<td>neuropathy</td>
<td>31 % (20 months)</td>
<td>HBAC – Tororo, Uganda</td>
</tr>
<tr>
<td>pancreatitis</td>
<td>0.3 % (20 months)</td>
<td>HBAC – Tororo, Uganda</td>
</tr>
<tr>
<td>lactic acidosis</td>
<td>0.1 % (20 months)</td>
<td>HBAC – Tororo, Uganda</td>
</tr>
<tr>
<td>d4T associated neuropathy and/or lipodystrophy</td>
<td>12.8% (median 14.4 months)</td>
<td>Cambodia</td>
</tr>
</tbody>
</table>
ZIDOVUDINE

ANAEMIA
Alternative causes of anaemia in HIV infectionRLS include

- HIV infection itself
- Mycobacteriuial infection (MAC)
- Malaria
- Drugs: Cotrimoxazole, Dapsone, Amphotericin B

Risk factors for Zidovudine related anaemia

- Low baseline haemoglobin
- Female gender
- Advanced HIV infection
- Malaria (esp in children)
- Concomitant use of other bone marrow suppressing drugs
Change in Haemoglobin after initiation of ZDV based ART

Women 65%; Median age 37 years

Median baseline CD4 count = 86 cells/mm³; WHO stage III - 56%  WHO stage IV - 23%

Median baseline Hb = 11.4 g/dl  Anaemia at baseline with Hb < 9.5 g/dl in 12%

Prevalence of anaemia at scheduled assessments – DART study cohort

Percentage

Weeks from ART initiation

Grade 1 8.0 to <9.5
Grade 2 7.0 to <8.0
Grade 3 6.5 to <7.0
Grade 4 <6.5 g/dl
## Zidovudine related Anaemia

<table>
<thead>
<tr>
<th>Clinically detectable &amp; reversible toxicity</th>
<th>Clinical Recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical symptoms &amp; signs</td>
</tr>
<tr>
<td></td>
<td>Lab : Haemoglobin level</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management</th>
<th>Safety monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient and provider education</td>
<td>Symptom driven investigation</td>
</tr>
<tr>
<td>Transfusion for severe cases</td>
<td>Routine monitoring of Hb</td>
</tr>
<tr>
<td>Stop CTX or other BM suppressant drugs</td>
<td>- at baseline</td>
</tr>
<tr>
<td>Substitution / pausing / lower does of ZDV</td>
<td>- at 4-12 weeks</td>
</tr>
</tbody>
</table>
TENOFOVIR

RENAL TOXICITY
Tenofevir related renal toxicity

Dysfunction of proximal renal tubules - unclear mechanism

“wasting” of substances normally reabsorbed in PT
- small proteins
- glucose
- phosphates
- bicarbonates

secondary glomerular dysfunction

Reduced Creatinine Clearance (CRF)
Disordered Bone Metabolism

Proteinuria
Glycosuria
Phosphaturia
Metabolic acidosis
## Tenofovir related renal toxicity

| Rare: 0.4% in one case series | Non-specific symptoms  
Progressive decline in eGFR |
|-------------------------------|---------------------------|
| **Risk factors:**  
Underlying renal disease  
Other nephrotoxic drugs  
Advanced HIV infection | **Lab:**  
Low potassium  
Low phosphates  
Clinical proteinuria  
Glycosuria (without raised blood glucose) |
| Often reversible on stopping TDF | **Recommended safety monitoring**  
Serum creatinine  - declines late  
Spot proteinuria probably not specific |
|  | Calculated Creatinine Clearance  
*Urine/protein creatinine ratio*  
*Serum Phosphate* |
Deriving estimated glomerular filtration rate (eGFR) using Serum-creatinine measurements

- **Cockcroft-Gault (CG):**
  
  \[
  (140 - \text{age}) \times \text{weight (kg)}
  \]
  
  \[
  \text{eGFR} = \frac{\text{Serum creatinine} \times 72}{(140 - \text{age}) \times \text{weight (kg)}} \times 0.85 \text{ (for women)}
  \]

- **Abbreviated MDRD study equation**

  \[
  \text{eGFR} = 186 \times S\text{-creatinine}^{1.154} \times \text{age}^{0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)}
  \]
Tenofovir & estimated GFR

Hand/wrist radiograph of patient at baseline & and after 24 weeks of TDF. Cortices appear thinner at 24 weeks, and there is decreased new trabecular bone in the areas under the growth plate (primary spongiosa. (ARROWS)

In this longitudinal study, children were on multiple drug ART and it is difficult to assign causality of loss in BMD unequivocally to TDF. Nevertheless, because patients who discontinued TDF while continuing their other drugs showed improvements in BMD, it is likely that TDF was responsible for at least some of the observed decreases in BMD. ... ... **TDF should be used with caution in growing children.**

*Gafni et al. Pediatrics 2006;118;711-718*
ABACAVIR

HYPERSENSITIVITY REACTION
# Abacavir HSR

<table>
<thead>
<tr>
<th>Potentially fatal HSR</th>
<th>Clinical Recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly within 1st 6 weeks of ART</td>
<td>Sudden onset of symptom pattern</td>
</tr>
<tr>
<td>Median onset within 11 days</td>
<td>Symptom escalation with each dose</td>
</tr>
<tr>
<td>Incidence: 5-6% in Europe/US studies</td>
<td>Resolution of symptoms within 48-72 hours of drug withdrawal</td>
</tr>
<tr>
<td>2% in DART cohort</td>
<td>Cutaneous patch testing</td>
</tr>
</tbody>
</table>

| Higher rates in ARV naïve patients | Genetic predisposition: HLAB5701 |
| Lower rates in African ethnic origin | |

<table>
<thead>
<tr>
<th>Management</th>
<th>Safety monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Once labelled always labelled”</td>
<td>Provider education</td>
</tr>
<tr>
<td>Stop ABC</td>
<td>Patient education</td>
</tr>
<tr>
<td>Never rechallenge with ABC</td>
<td>(Patient warning card)</td>
</tr>
</tbody>
</table>
Example of Patient Safety Warning Card utilised in the DART study cohort

[Boxed text]

**IMPORTANT - ALERT CARD**

**ZIAGEN™ (abacavir) Tablets**

Patients taking Ziagen may develop a hypersensitivity reaction (serious allergic reaction) which can be life threatening if treatment with Ziagen is continued.

**CONTACT YOUR DOCTOR IMMEDIATELY** for advice on whether you should stop taking ZIAGEN if:

1. You get a skin rash OR
2. You get one or more symptoms from at least two of the following groups:
   - fever
   - shortness of breath, sore throat or cough
   - nausea or vomiting or diarrhoea or abdominal pain
   - severe tiredness or achiness or generally feeling ill

If you have discontinued Ziagen due to this reaction, **YOU MUST NEVER TAKE** Ziagen or any other another medicine containing abacavir (TRIZIVIR) again. as **within hours** you may experience a life-threatening reaction.

(see reverse of card)