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Our Issues, Our Drugs, Our Patients

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Pharmacovigilance:

Emtricitabine Induced Thyrotoxicosis
&
Associated Hair Loss

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Epidemiologist/Biostatistician
Presentation Format

• Brief About Piet Retief Pharmacovigilance Committee
• Case description
• Discussion
• Conclusion
• Recommendation
Pharmacovigilance at Piet Retief Hospital

• Established Committee in June 2012
  – Support from National Pharmacovigilance Unit of Department of Health
  – Mpumalanga Pharmacovigilance Unit
  – Fully integrated in HIV/TB program in hospital and 11 primary health care facilities

• Primary objective:
  – To ensure patient safety while on HIV/TB treatment by identifying, documenting and managing adverse events
Pharmacovigilance Committee Structure

Piet Retief Hospital (Wellness) ACC

Pharmacy - coordination

Family Physician - Chairs

Partners (BRHC)

11 PHC Facilities

National/Provincial/District

Contract signed with CEO
Case Description

• This is a 38-year-old female patient on antiretroviral treatment.
• She was initiated on individual three-drug highly active antiretroviral treatment (HAART) regimen in Jan 2011
  – Tenofovir, Lamivudine and Efavirenz
  – NIMART system
• In August 2014;
  – the fixed dosed combination regimen was started.
  – Tenofovir, Emtricitabine and Efavirenz
  – Regimen shift to FDC in line with new HIV guidelines
• Emtricitabine replaced lamivudine in the fixed dose combination
Case Description

• Six months into the new regimen,
  – She noticed hair on her head was thinner
  – Brittle and increasing falling when combing.
  – This was followed by global loss of hair on the head.
  – The pubic and axillar hairs were spared.
  – Giotre
Case Description

• In addition clinical features

  – She developed proptosis, with progressive enlargement of the eyeball

  – Followed by:
    • Mild pain on the right eye
    • Tearing of both eye and
    • Photophobia.
Other Associated Clinical Features

- Fatigue
- Weight loss despite increase appetite
- Intolerance to heat and mildly enlarged breast.
- The palms are always moist.
Clinical Assessment

• 38 year old RVD patient with
  – Emtricitabine Induced hair Loss
  – Emtricitabine Induced Thyrotoxicosis
    • Thyroid enlargement
# Drug Exposure

<table>
<thead>
<tr>
<th>Date</th>
<th>Regimen/Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>05 January 2011</td>
<td>Tenofovir 300mg daily Lamivudine 300mg daily Efavirenz 600mg daily</td>
<td>Individual drugs Stopped on 05 August 2013. No adverse event reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>05 August 2014</td>
<td>Isoniazid 300mg daily</td>
<td>6 month prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenofovir 300mg daily Ematricitabine 200mg daily Efavirenz 600mg daily</td>
<td>Alopecia Mild gynaecomastia Proptosis (Thyrotoxicosis)</td>
</tr>
</tbody>
</table>
At Presentation (Referral)

Global Hair Loss

Proptosis

Giotre

Permission Granted to Show Face for Purpose of this Presentation

Treatment Stop, Investigation Started
One week later – all treatment stopped

Proptosis showed visible Improvement
Facial expression showed less Anxiety
Six Months Later

Regimen: Tenofovir, Abacavir and Efavirenz
Others: Carbimazole

Proptosis resolved
Gynaecomastia resolved
Hair Growth resumed
## Laboratory Findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>Six Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Values</td>
<td>Observed Values</td>
</tr>
<tr>
<td>TSH</td>
<td>0.34 – 5.6</td>
<td>0.01 L mIU/l</td>
</tr>
<tr>
<td>Free T4</td>
<td>7.6 – 16.1</td>
<td>20.7 H pmol/l</td>
</tr>
<tr>
<td>Free T3</td>
<td>3.9 – 6.7</td>
<td>5.6 pmol/l</td>
</tr>
</tbody>
</table>

At baseline TSH Suppressed, T4 elevated, T3 normal
## Blood Cells and Chemistry - Unaffected

<table>
<thead>
<tr>
<th>Tests</th>
<th>Normal Values</th>
<th>Observed values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute CD4</td>
<td>500 – 2010 X 10^6/l</td>
<td>792</td>
</tr>
<tr>
<td>Viral Load</td>
<td>&lt;20 Copies ((Roches Cobas Ampliprep)</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Creatinine</td>
<td>60 – 100 umol/l</td>
<td>37</td>
</tr>
<tr>
<td>eGFR</td>
<td>&gt;60 ml/min/1.73sqm</td>
<td>&gt;60</td>
</tr>
<tr>
<td>ALT</td>
<td>7 -35 U/l</td>
<td>26</td>
</tr>
<tr>
<td>HB</td>
<td><strong>12.1 – 16.3 g/dl</strong></td>
<td><strong>11.8</strong></td>
</tr>
<tr>
<td>MCV</td>
<td>Low (83 – 101)</td>
<td>77.0 fl</td>
</tr>
<tr>
<td>MCH</td>
<td>Low (27 -32)</td>
<td>26.7 pg</td>
</tr>
<tr>
<td>Immunoglobulin G</td>
<td>15.00g/l</td>
<td>7.00 – 16.00</td>
</tr>
<tr>
<td>Immunoglobulin A</td>
<td>1.90 g/l</td>
<td>0.70 – 4.00</td>
</tr>
<tr>
<td>Immunoglobulin M</td>
<td>0.54 g/l</td>
<td>0.40 – 2.30</td>
</tr>
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</table>
Discussion: Emtricitabine in Public Health Sector

• In South Africa HIV Program
  – Emtricitabine in the public sector HIV program is a fixed dose combination treatment with Tenofovir and Efavirenz.

• It is therefore difficult to isolate the adverse events due to Emtricitabine
  – unless there is pharmacovigilance program to monitor adverse events and
  – apply diagnosis of exclusion.
Why Was Emtricitabine the Suspected Drug?

• A 38-year old female on Tenofovir, Lamivudine and Efavirenz developed thyrotoxicosis and hair loss a few months into fixed dosed combination
  – Emtricitabine was the only new drug introduced.
  – The patient recovered fully when Emtricitabine was removed
Could it have been other drugs?

• The patient was exposed to two other ARVs drugs and still on them
  – Tenofovir 300mg daily
  – Efavirenz 600mg

• Also exposed to IPT
  – Isoniazid 300mg for six months in 2011
Lamivudine Induced Hair Loss: Confined to the centre of the head, Alopecia Areata
What is known of Emtricitabine Adverse events?

• Symptomatic side effects of emtricitabine may be difficult to distinguish from those of other antiretrovirals with which it is combined.

• The most common adverse effects noted in clinical trials of emtricitabine with other antiviral agents were:
  – headache, diarrhea, nausea, and rash.
Emtricitabine Side Effects

• Side effects were seldom severe
  – approximately 1% of participants discontinuing participation because of these events.

  – Skin discoloration, manifested by hyperpigmentation of the palms or soles, or both, and generally mild and asymptomatic
Emtricitabine Side Effects

• Is a nucleoside analogues
  – May be associated with mitochondrial toxicity leading to potentially serious long-term side effects such as lactic acidosis and disorders of lipid metabolism
    • The extent to which emtricitabine may contribute to such effects is not known.
• Resistance to emtricitabine may develop with only a single viral mutation in the setting of suboptimal viral suppression.
Drug Interactions

- Emtricitabine does not appear to interact significantly with enzymes involved in drug metabolism.
- Clinically significant drug-drug interactions involving emtricitabine have not been identified.
Conclusion

• Pharmacovigilance and documentation of adverse events allows identification rare events
  – Allows early identification
  – Allows prompt management
  – Empowers care and treatment teams (CCMT)
Recommendations

• Integrate Pharmacovigilance with documentation of adverse events into routine NIMART and Advance Clinical Care programs
Thank You

• The Patient – allowed pictures

• Department of Health
  – National Pharmacovigilance Unit in NDOH
  – Mpumalanga Provincial Pharmacovigilance Unit
  – Gert Sibande District HAST
  – Hospital and PHC management
  – Pharmacovigilance Committee – Robust & Progressive discussion of cases (Mixed NIMART & ACC)

• BROADREACH HealthCare