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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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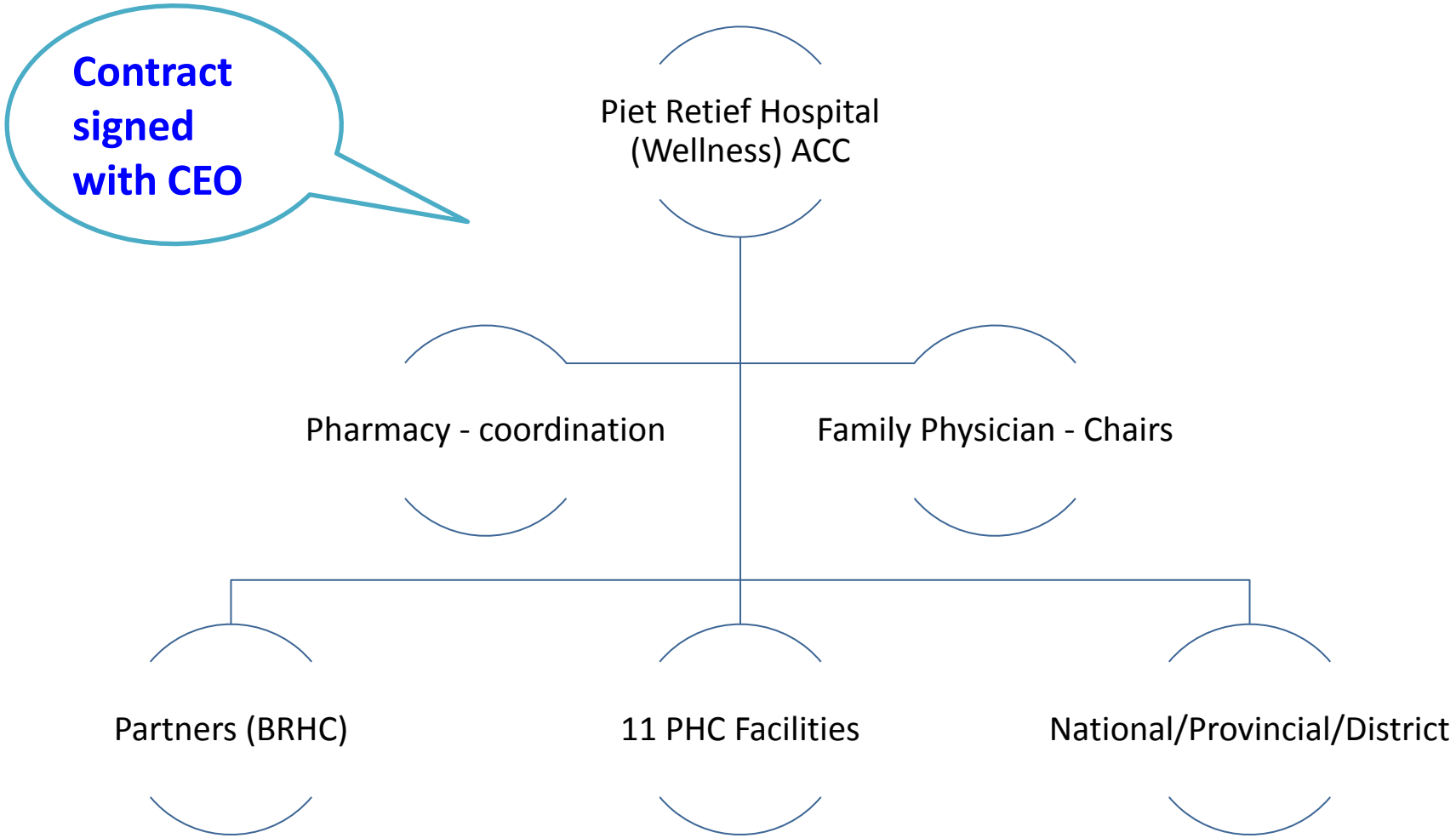
Presentation Format

- 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



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
- Ematricibine 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 axillary 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

Date	Regimen/Drug	Comment
05 January 2011	Tenofovir 300mg daily Lamivudine 300mg daily Efavirenz 600mg daily	Individual drugs Stopped on 05 August 2013. No adverse event reported
	Isoniazid 300mg daily	6 month prophylaxis
05 August 2014	Tenofovir 300mg daily Ematricitabine 200mg daily Efavirenz 600mg daily	Alopecia Mild gynaecomastia Proptosis (Thyrotoxicosis)

At Presentation (Referral)

Global Hair Loss

Proptosis

Permission Granted to Show Face for Purpose of this Presentation

Giotre

Treatment Stop, Investigation Started

One week later – all treatment stopped

Proptosis showed visible Improvement Facial expression showed less Anxiety

Six Months Later

Proptosis resolved
Gynaecomastia resolved
Hair Growth resumed

Regimen: Tenofovir, Abacavir and Efavirenz
Others: Carbimazole

Laboratory Findings

Test	Baseline		Six Months
	Normal Values	Observed Values	Observed Values
TSH	**0.34 – 5.6**	**0.01 L mIU/l**	**1.04 mIU/L**
Free T4	**7.6 – 16.1**	**20.7 H pmol/l**	**12.3 pmol/L**
Free T3	3.9 – 6.7	5.6 pmol/l	3.4 pmol/L

At baseline TSH Suppressed, T4 elevated, T3 normal

Blood Cells and Chemistry - Unaffected

Tests	Normal Values	Observed values
Absolute CD4	500 – 2010 X 10^6/l	792
Viral Load	<20 Copies ((Roches Cobas Ampliprep)	<20
Creatinine	60 – 100 umol/l	37
eGFR	>60 ml/min/1.73sqm	>60
ALT	7 -35 U/l	26
HB	**12.1 – 16.3 g/dl**	**11.8**
MCV	Low (83 – 101)	77.0 fl
MCH	Low (27 -32)	26.7 pg
Immunoglobulin G	15.00g/l	7.00 – 16.00
Immunoglobulin A	1.90 g/l	0.70 – 4.00
Immunoglobulin M	0.54 g/l	0.40 – 2.30

Discussion: Emtricitabine in Public Health Sector

- In South Africa HIV Program
  - Emtricibine 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 Ematricibine
  - unless there is pharmacovigilance program to monitor adverse events and
  - apply diagnosis of exclusion.

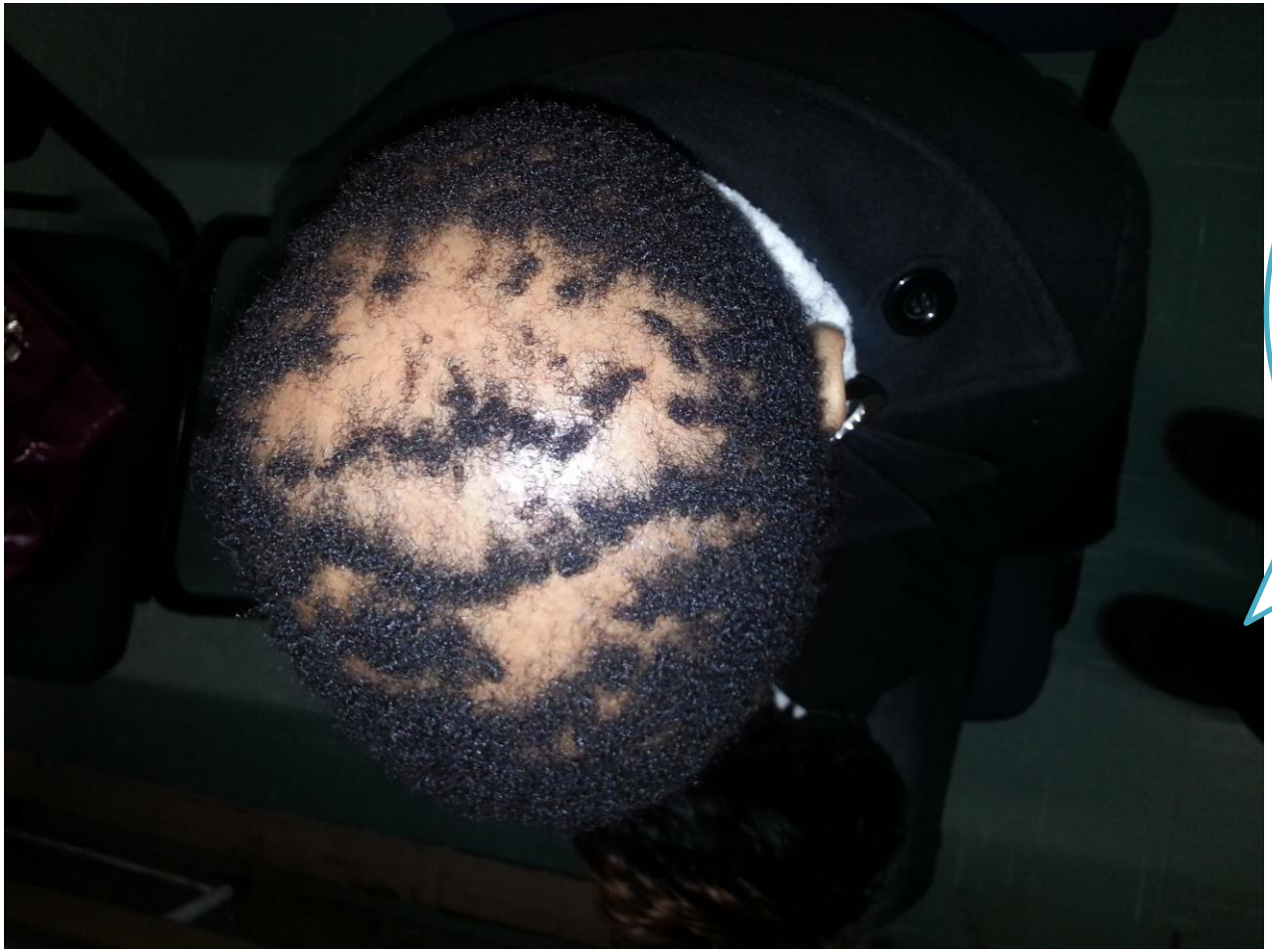
Why Was Emtricitabine the Suspected Drug?

- A 38-year old female on Tenofovir, Lamivudine and Efavirenz developed thyrotoxicosis and hair loss a few months into fixed dosed combination
  - Ematricibine 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



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

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