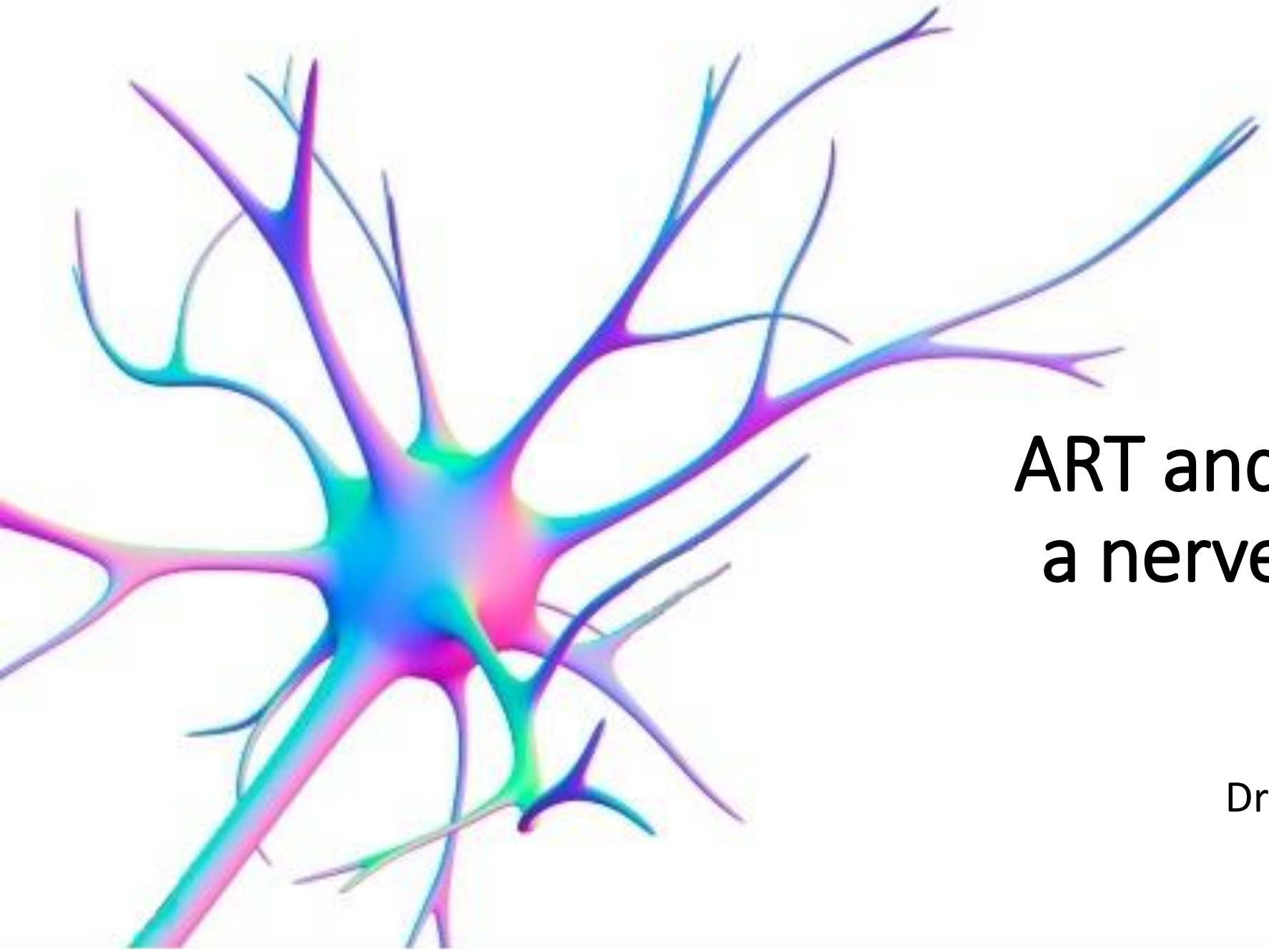
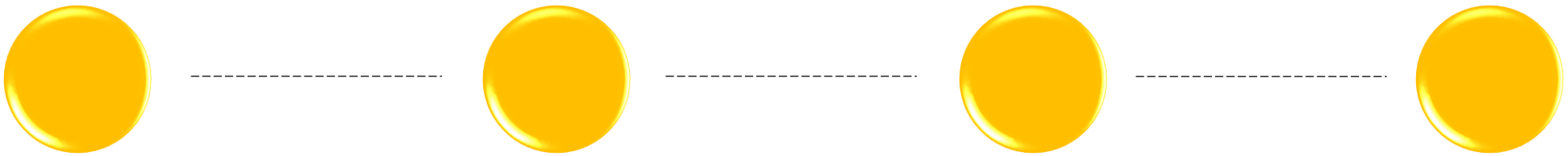


ART and TB treatment, a nerve wracking mix

Dr Prudence Ive

Patient E-C a 26 year old man



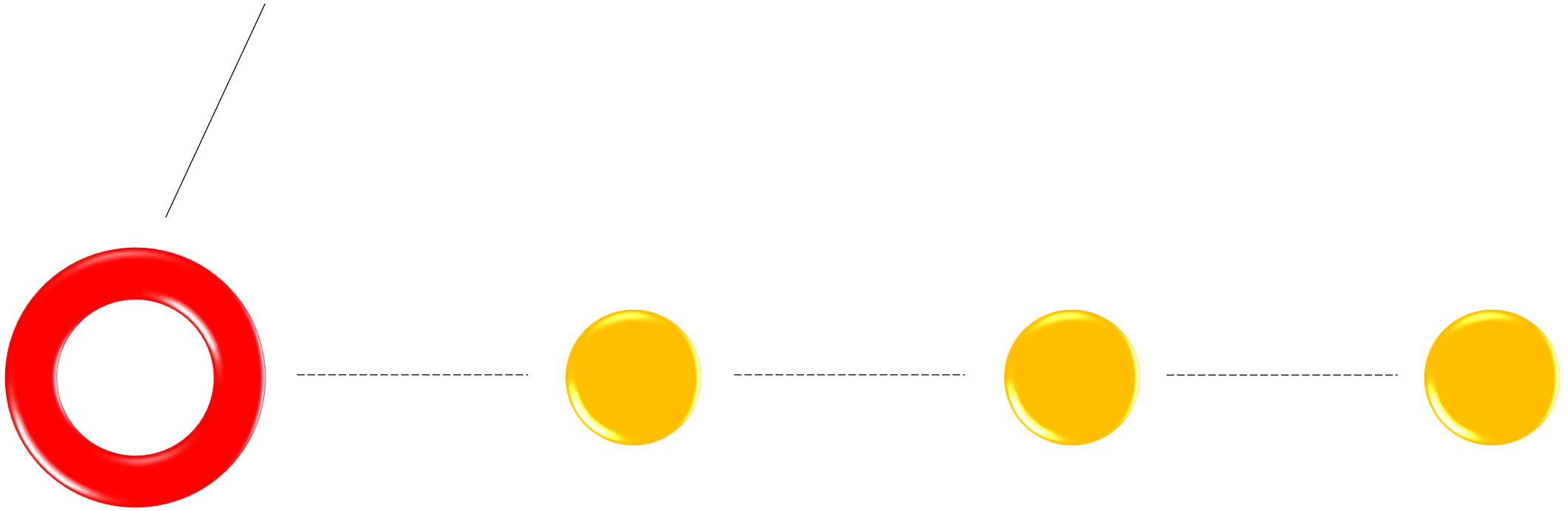
2 years ago

1 month ago

2 weeks ago

On admission

His past medical history included an admission to GSH for head trauma.



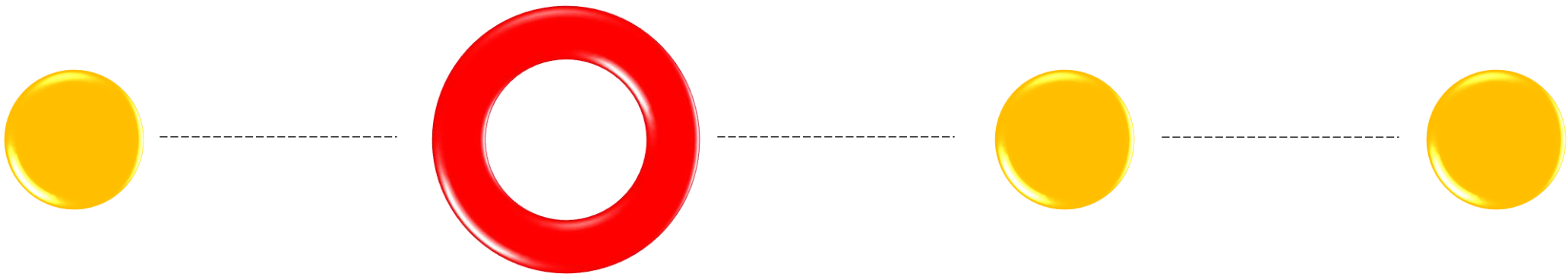
2 years ago

1 month ago

2 weeks ago

On admission

Diagnosed with disseminated tuberculosis
TB was resistant to INH (culture with PCR showing KatG)
Initiated on RHZE (per weight of 55kg)



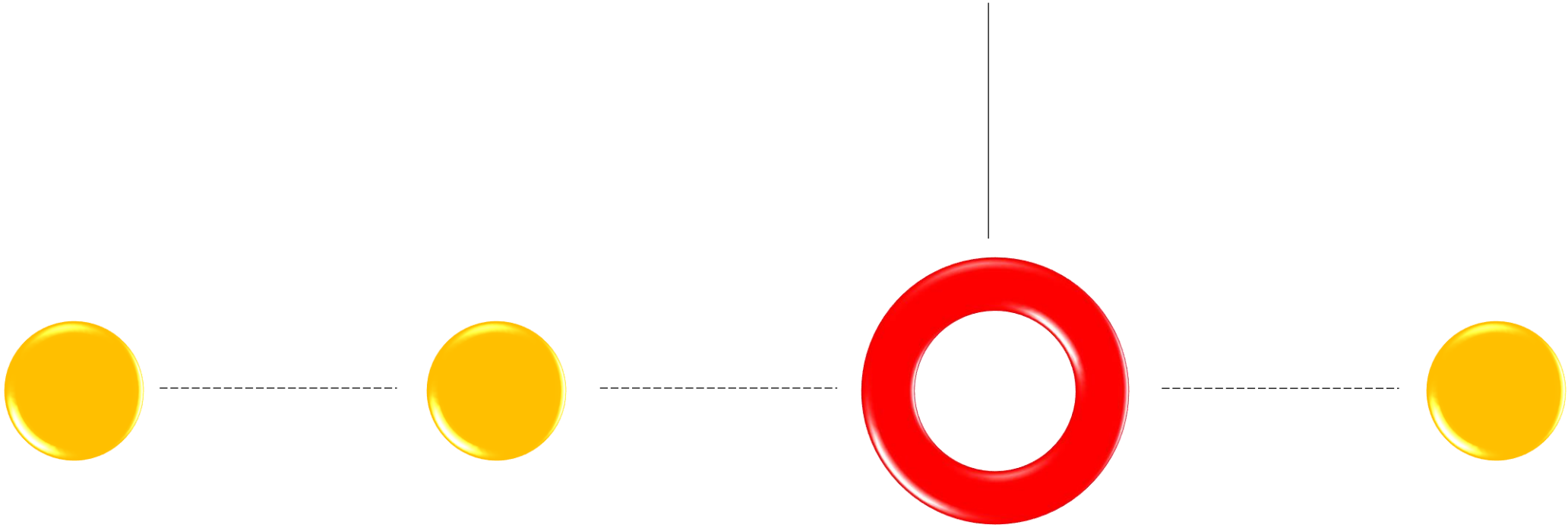
2 years ago

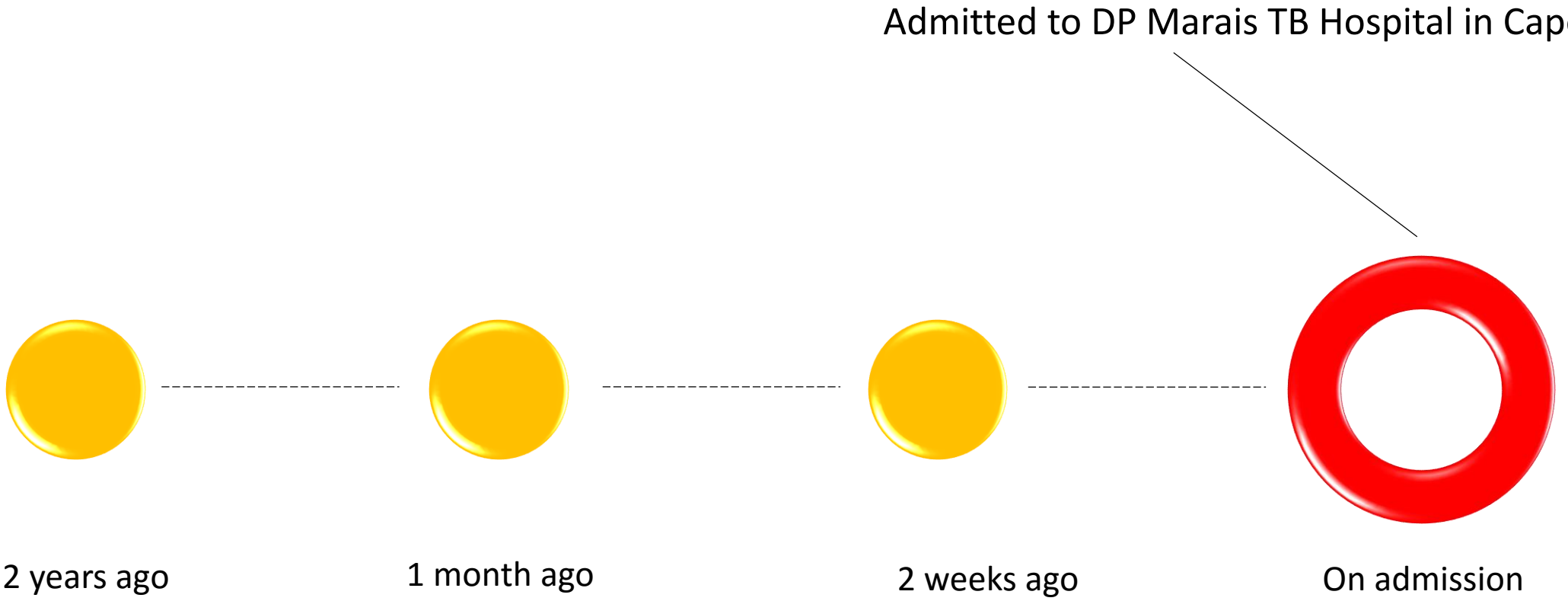
1 month ago

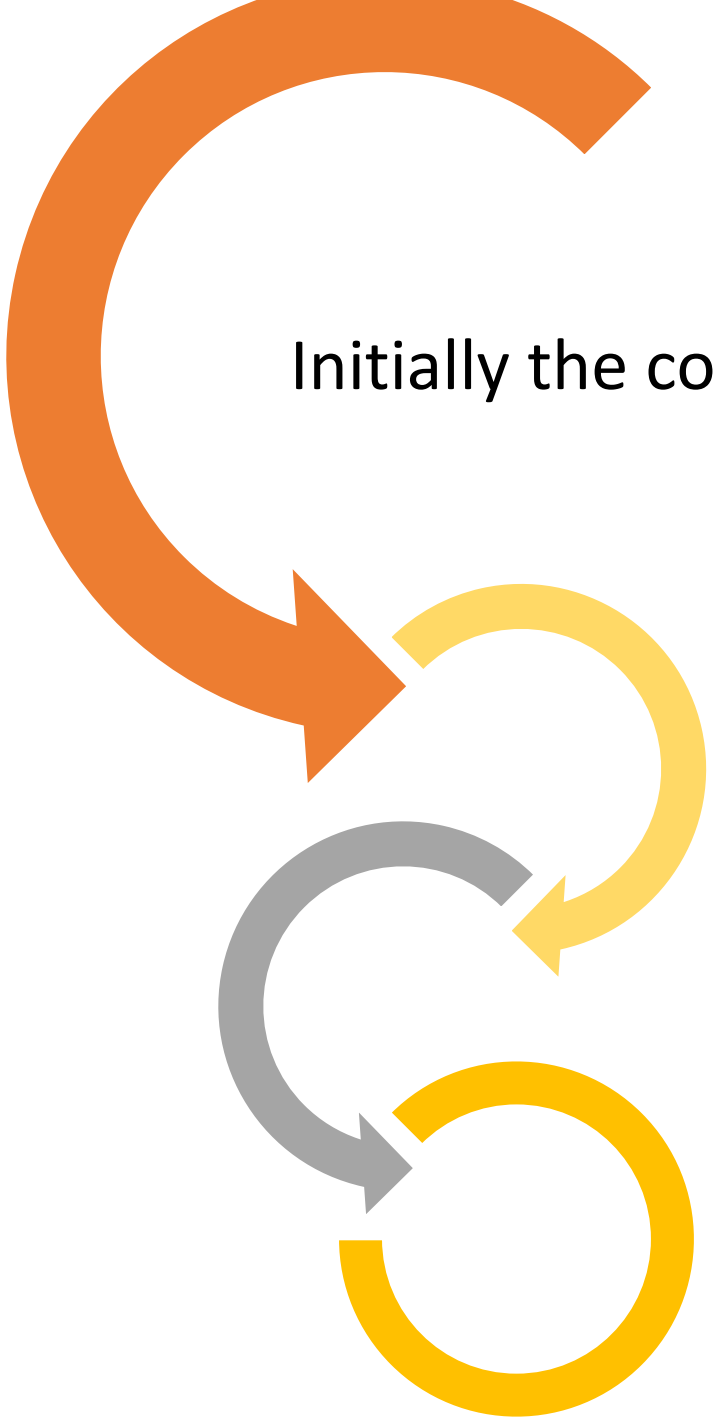
2 weeks ago

On admission

HIV positive with a nadir CD4 count of 16. Initiated antiretroviral therapy with tenofovir, emtricitabine and efavirenz at the local clinic

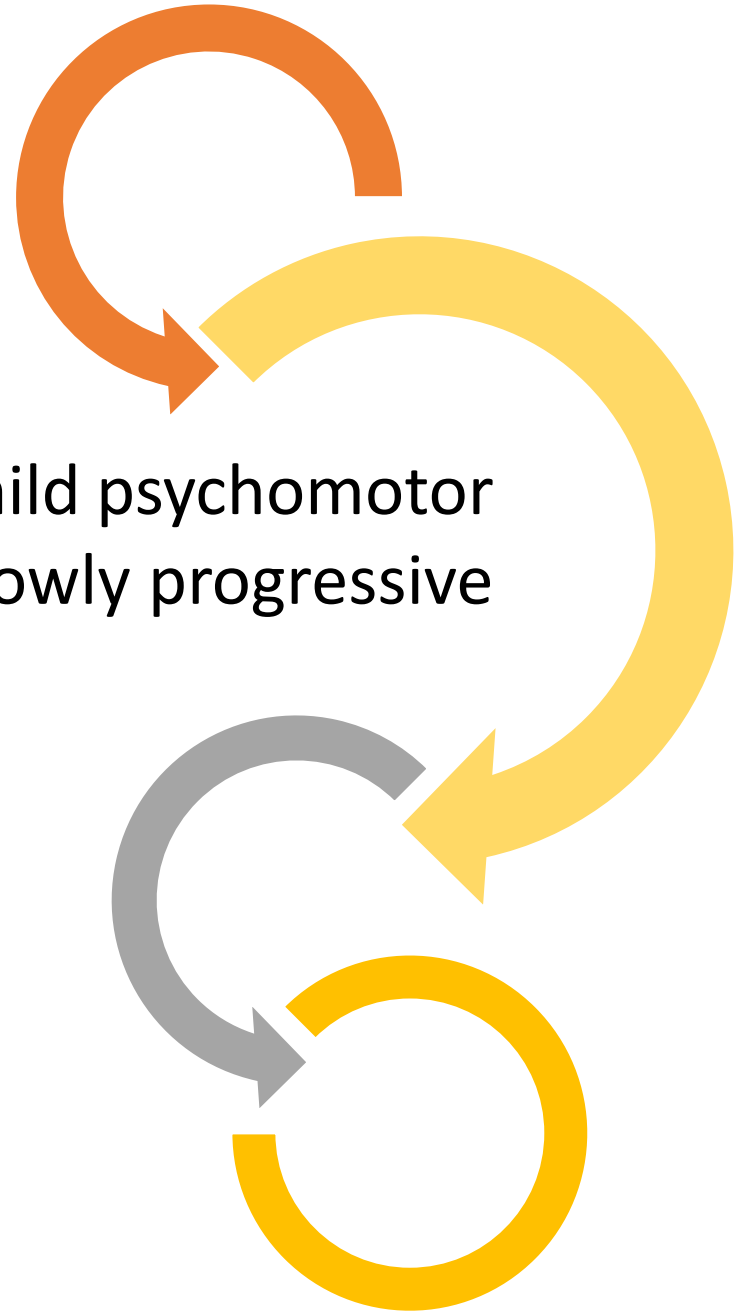


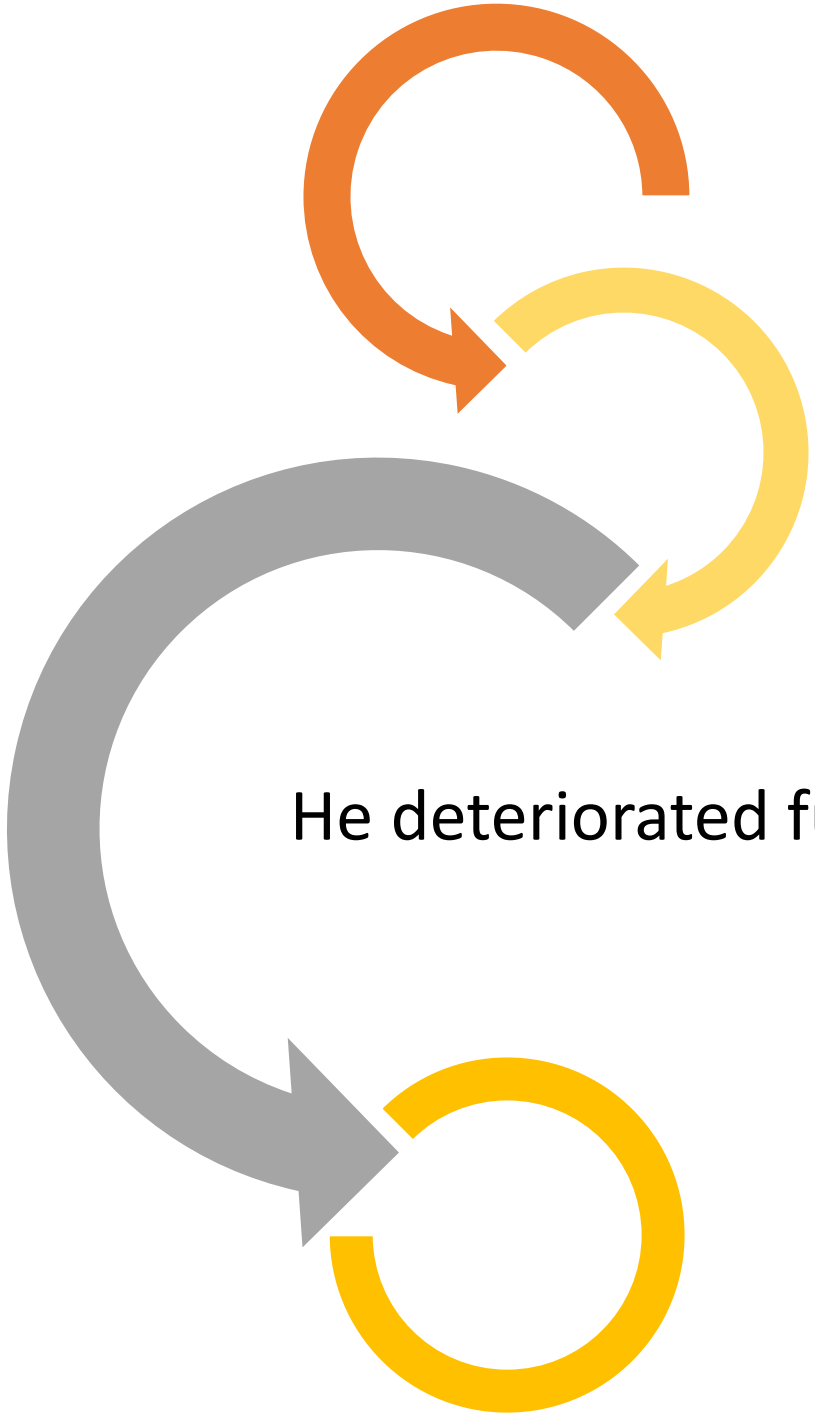

Admitted to DP Marais TB Hospital in Cape Town
2 years ago
1 month ago
2 weeks ago
On admission



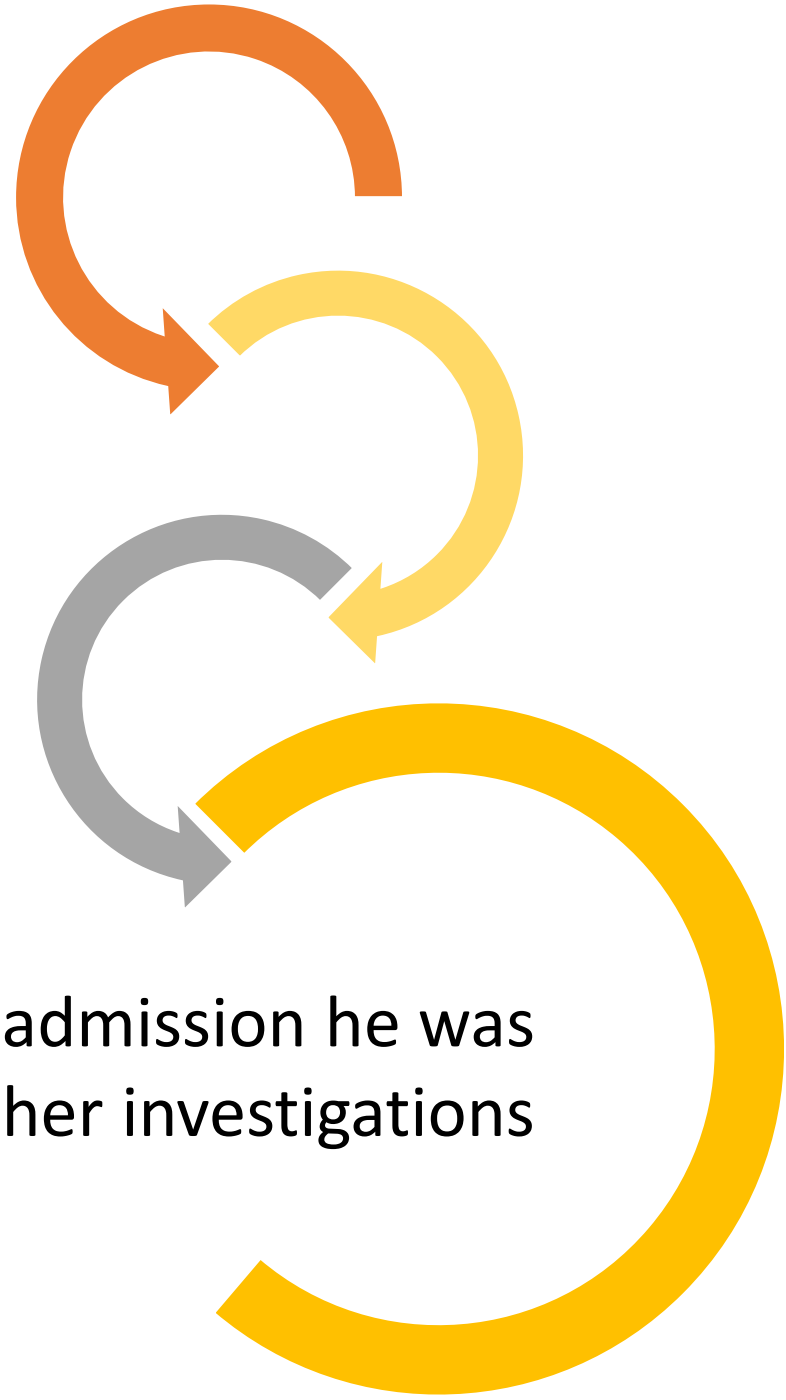
Initially the condition of the patient improved

During the course of his admission he developed mild psychomotor retardation which was slowly progressive





He deteriorated further and also developed ataxia



A month after his admission he was referred back to his local hospital for further investigations

Differential Diagnosis

INFECTIOUS

- Tuberculous meningitis/tuberculoma +/- IRIS
- Cryptococcal meningitis
- CNS toxoplasmosis
- HIV associated dementia
- Cytomegalovirus encephalitis
- Neurosyphilis
- Progressive multifocal leukoencephalopathy

TUMOURS

- CNS lymphoma

METABOLIC/ENDOCRINE

- B12 deficiency
- Thyroid disease
- Adrenal insufficiency

SUBSTANCE WITHDRAWL OR INTOXICATION

- Chronic methamphetamine
- Opioids
- Chronic cannabis

MEDICATIONS

- Antiretroviral therapy
- Drug-drug interactions

Investigations

BLOODS

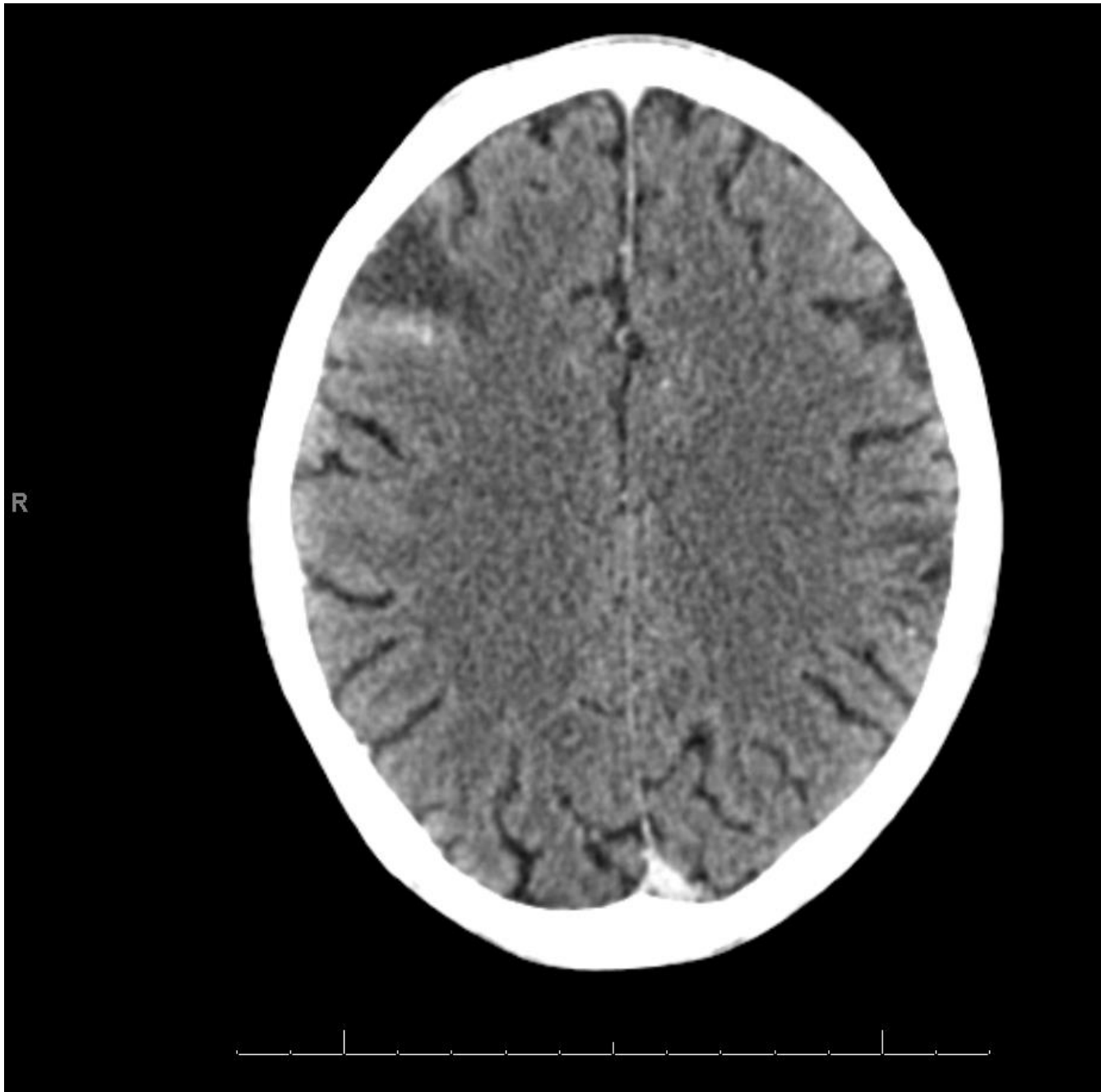
- U&E normal
- LFT normal
- Serum CLAT neg,
- TPHA neg,
- B12- 421
- T4 normal
- CSF: CLAT neg and nil of note

CSF

- Glucose- 4.0
- Protein-0.32
- Polymorphs-0
- Lymphocytes-0
- Ertythrocytes-260
- CLAT neg
- No bacteria observed, no bacterial growth

Investigations

Patient had a CT Brain scan which showed right frontal and left parietal encephalomalacia in keeping with previous trauma as well as generalised age inappropriate atrophy.



Progress

- The patient’s condition continued to deteriorate with further psychomotor retardation and slowing
- He became obtunded with no focal signs
- No signs of sepsis
- Efavirenz was interrupted and he was transferred to a tertiary hospital where he died on the day of arrival, probably due to aspiration.
- Efavirenz level was >20 mg/l

Side Effects of efavirenz per package insert

- CNS effects: (eg, abnormal dreams, insomnia, impaired concentration, hallucinations, dizziness or drowsiness)
  - usually begin within 1 to 2 days after starting efavirenz, and generally resolve within 2 to 4 weeks of continued therapy
- Psychiatric effects: Serious psychiatric side effects have been associated with use, including aggressive behaviour, severe depression, suicidal ideation, nonfatal suicide attempts, paranoia, and mania
  - use with caution in patients with a history of mental illness/drug abuse (predisposition to psychological reactions)
- Incidence of neuropsychiatric side effects correlated with plasma concentrations[1]

1.Kenedi C, Goforth H. AIDS Behav 2011;15:1803

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2012.04299.x

Letter to the Editors

Severe efavirenz-induced vacuolar axonopathy complicated by fatal aspiration pneumonia

Chris Kenyon,[1] Sipho Mfolozi,[2] Roland Croxford,[3] Robert Colebunders[5] & Karen Cohen[4]

[1]Pieter de Coninickstraat 5, Antwerpen, Belgium, Departments of [2]Pathology, [3]Medicine, [4]Pharmacology, University of Cape Town, Cape Town, South Africa and [5]Head clinical HIV/STD Unit, Institute of Tropical Medicine, University of Antwerp (UA), Antwerp, Belgium

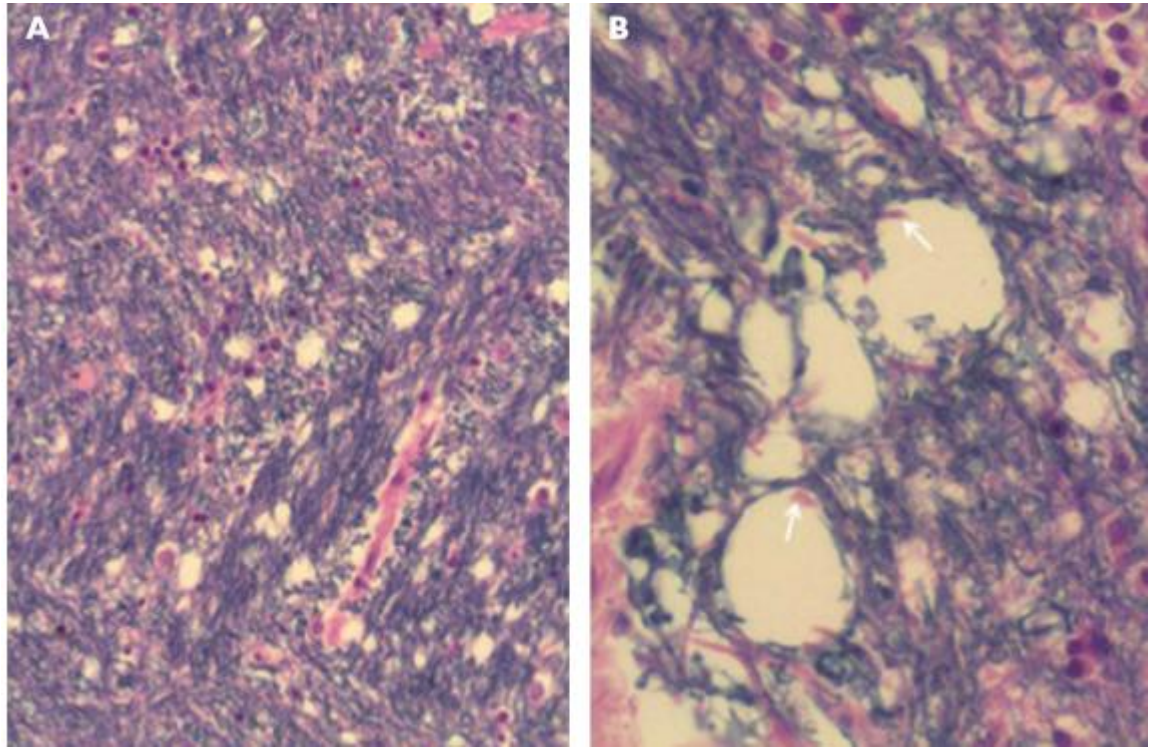
Similarities of the case

- Efavirenz based ART of 3 months and concomitant RHZE of 1 month
- Low BMI of 17.4 kg m^{-2}
- Mental slowing with apathy and drowsiness
- Ataxia but no other focal neurology
- 3 s gap between an instruction and response
- Progressively more drowsy and inability to swallow normally
- Aspirated and died
- Efavirenz stopped and changed to nevirapine

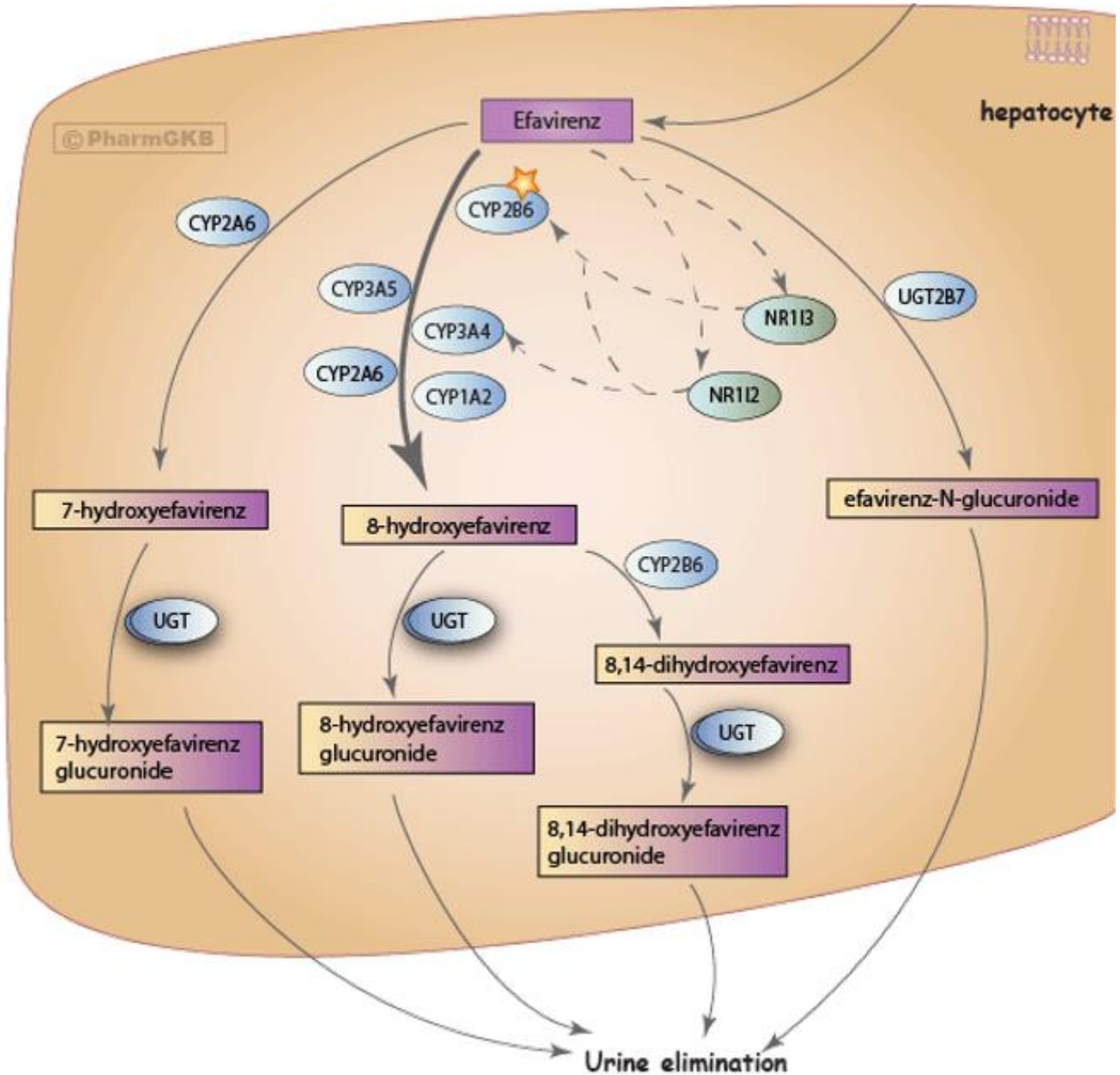
- Efavirenz level of 13.7 mg/l

  (5 days after stopping)

- Extensive axonal vacuolopathy in the central white matter and particularly in the dentate nuclei



- Mitochondriopathy due to efavirenz
- Mainly shown in hepatocytes
  - Direct effect on mitochondria through different mechanism than DNA polymerase gamma



CYP2B6 is the main enzyme involved in efavirenz metabolism

Polymorphisms in the *CYP2B6* gene associated with differences in efavirenz PK parameters

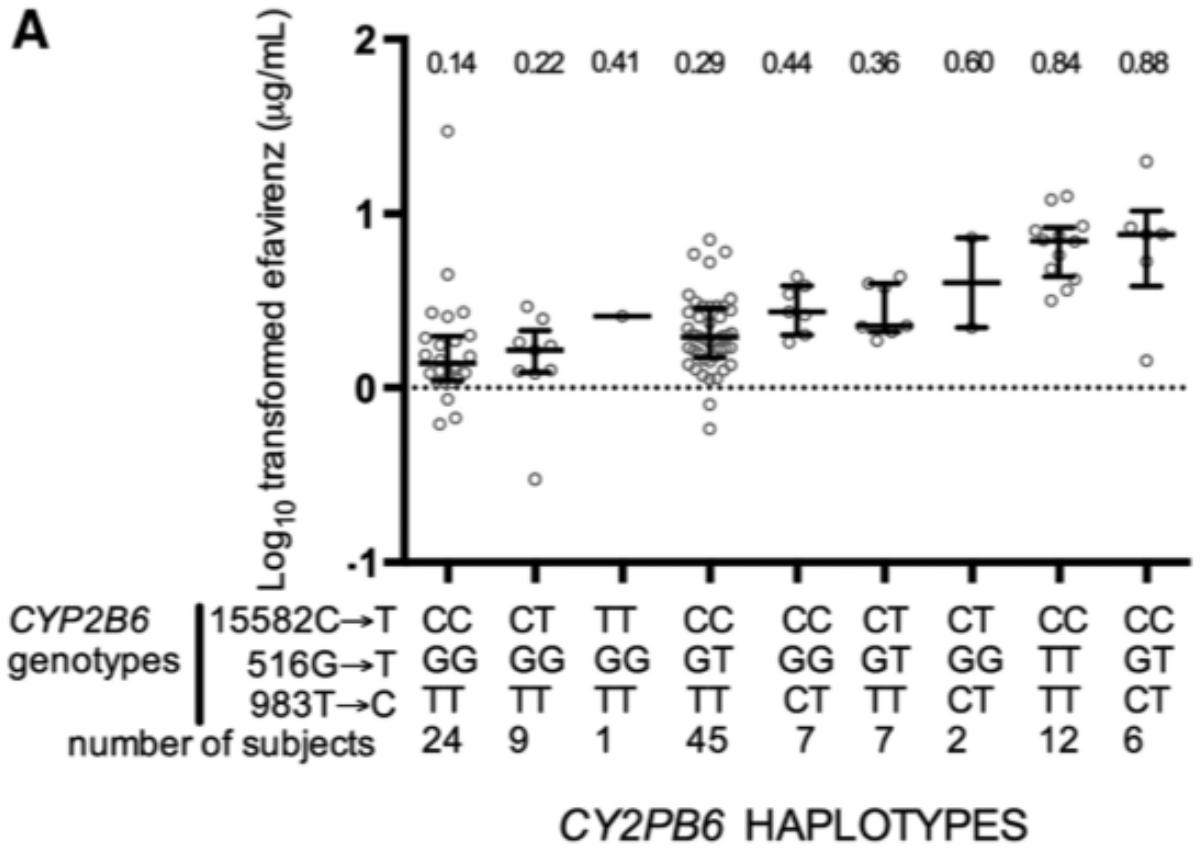
PharmGKB and Stanford University

BJCP British Journal of Clinical Pharmacology

Pharmacogenetics of plasma efavirenz exposure in HIV-infected adults and children in South Africa

Phumla Z. Sinxadi,[1] Paul D. Leger,[2] Helen M. McIlleron,[1] Peter J. Smith,[1] Joel A. Dave,[3] Naomi S Levitt,[3] Gary Maartens[1] & David W. Haas[4]

[1]Division of Clinical of Pharmacology and [3]Division of Exercise and Endocrine Metabolism, Department of Medicine, University of Cape Town, Cape Town, South Africa, [2]Vanderbilt University Medical Center and [4]School of Medicine, Department of Medicine, Nashville, Tennessee, United States of America



RESULTS

Among 113 participants (59 adults and 54 children), minor allele frequencies for *CYP2B6* 516G→T, 983T→C, and 15582C→T [rs4803419] were 0.36, 0.07, and 0.09, respectively. Based on composite *CYP2B6* 15582/516/983 genotype, there were 33 extensive metabolizer, 62 intermediate metabolizer and 18 slow metabolizer

Br J Clin Pharmacol 2015. 80:1 146-156

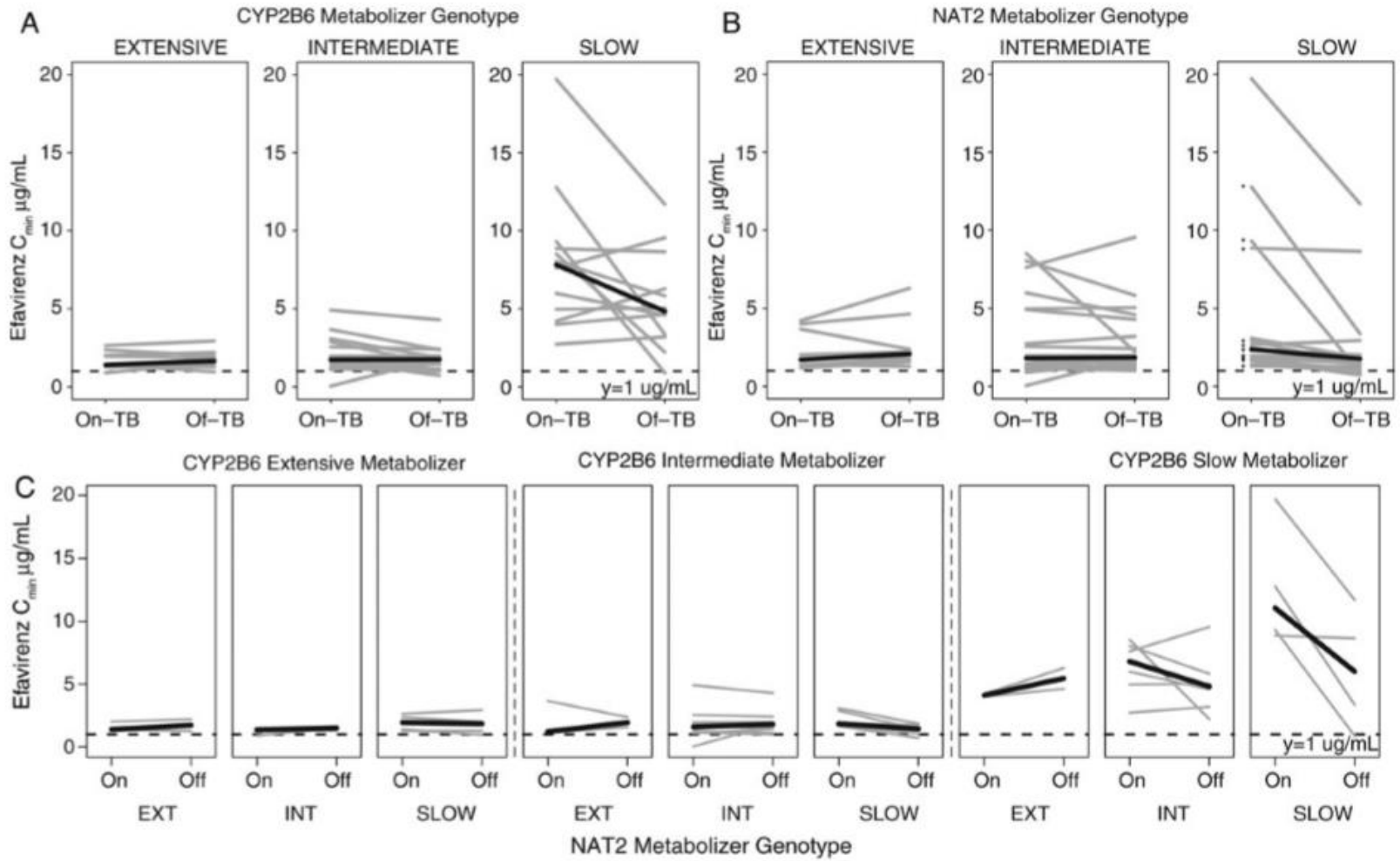
HIV/AIDS BRIEF REPORT

Combined Effect of *CYP2B6* and *NAT2* Genotype on Plasma Efavirenz Exposure During Rifampin-based Antituberculosis Therapy in the STRIDE Study

Anne F. Luetkemeyer,[1] Susan L. Rosenkranz,[2] Darlene Lu,[2] Beatriz Grinsztejn,[3] Jorge Sanchez,[4] Michael Ssemmanda,[5] Ian Sanne,[6] Helen McIlleron,[7] Diane V. Havlir,[1] and David W. Haas[8]; for the Adult AIDS Clinical Trials Group A5221 and A5243 Study Teams

Clinical Infectious Diseases® 2015;60(12):1860–3

In STRIDE, slow metabolizer *CYP2B6* and *NAT2* genotypes were each associated with increased plasma efavirenz concentrations during antituberculosis therapy. Concentrations were greater on therapy than off therapy in 58% with *CYP2B6* and 93% with *NAT2* slow metabolizer genotypes. Individuals with slow metabolizer genotypes in both genes had markedly elevated concentrations.



Dhoro et al. BMC Pharmacology and Toxicology (2015) 16:4
DOI 10.1186/s40360-015-0004-2

BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

*CYP2B6*6, CYP2B6*18*, Body weight and sex are predictors of efavirenz pharmacokinetics and treatment response: population pharmacokinetic modeling in an HIV/AIDS and TB cohort in Zimbabwe

Milcah Dhoro[1,2*], Simbarashe Zvada[3], Bernard Ngara[1], Charles Nhachi[2], Gerald Kadzirange[4], Prosper Chonzi[5] and Collen Masimirembwa[1]

There was a 21% increase in efavirenz clearance for every 10kg increase in weight

Table 5 Proposed optimal doses given *CYP2B6* genotypes, weight and gender

Variable		Females		Males	
		<58 kg	>58 kg	<58 kg	>58 kg
CYP2B6*18	CYP2B6*6	1 -4 μg/ml	1 -4 μg/ml	1 -4 μg/ml	1 -4 μg/ml
TT	GG	400	400	400	400
TT	GT	200	200	200	200
TT	TT	200	200	200	200
TC	GG	400	400	400	400
TC	GT	400	200	200	200
TC	TT	200	200	200	200
CC	GG	400	600	600	600
CC	GT	200	300	300	300
CC	TT	200	200	200	200

Efavirenz toxicity in HIV and TB coinfection

Prudence Ive[1], Chloé Plumettaz[1], Roland Croxford[2], Janet Scott[2], Tom Boyles[1]

[1]Division of Infectious Diseases and HIV medicine, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
[2]DP Marais Hospital, Metro TB Complex, Department of Health Western Cape

Introduction

- Efavirenz toxicity has been well documented with extreme cases resulting in death
- High risk in patients who are slow metabolisers with polymorphisms of *CYP2B6* and *NAT2* associated with isoniazid as shown in the South African population

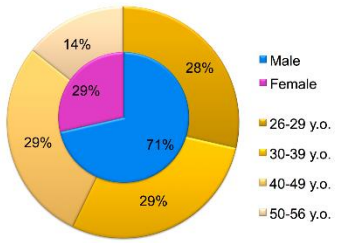
Method

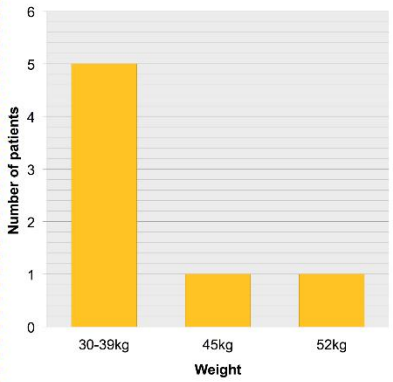
- Observational retrospective review from June 2014 to June 2015 of patients at DP Marais TB Hospital in the Western Cape receiving efavirenz and therapy for tuberculosis with elevated blood levels of efavirenz.

Results

- 7 patients were found to have efavirenz levels greater than 4 mg/L.
- Levels ranged from 7.4 mg/L to greater than 20 mg/L, in 4 of the patients.
- 5 of the patients were male.
- The average age was 37 years (range 27-56 years).
- The mean weight was 40kg (range 32-52kg) and for 2 patients where height was available the body mass index was 13 and 14 respectively.
- 6 of the patients were on standard treatment for drug susceptible tuberculosis, and 1 patient was receiving treatment for drug resistant tuberculosis but the regimen included isoniazid.
- No patients had liver or renal dysfunction.

BASELINE CHARACTERISTICS





Patient		Age (years)	Gender	Weight (kg)	Co Morbidities	Dose EFV (mg)	TB treatment regimen	CD4 (¢/µL)	Hb (g/dL)	ALT/ AST (U/L)	Creatinine (µmol/L)
1	♂	26	M	45	Nil	600	RHZE	16	13.8	N	N
2	♂	46	M	52	Peripheral neuropathy feet	600	RHZE	94	8.1	N	N
3	♀	32	F	35	Depression	600	RHZE	16	7.9	N	N
4	♂	56	M	37	Nil	600	RHZE	66	9.6	N	N
5	♂	43	M	32 *BMI: 13.9 kg/m²*	Nil	600 ⇩ 400	RHZE	39	9.9	N	N
6	♂	30	M	36 *BMI: 12.8 kg/m²*	Seizures	600	H + MDR	1	6.5	N	N
7	♀	27	F	39	Nil	600	RHZE	96	9.6	N	N

♀: female ♂: male

EFV: efavirenz; TB: tuberculosis; RHZE: rifampicin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E); MDR: multi drug resistant tuberculosis treatment containing kanamycin, moxifloxacin, ethionamide, terizidone, pyrazinamide; N: normal range