Adult cases

Dr BI Gosnell

Case 1

- White female in her early forties.
- Presented to a peripheral hospital with bruising and gum bleeding.
- FBC: WCC 4.8, Hb 9.2, Plt 47.
- During work-up found to be HIV positive. Baseline CD4 27.
- Thrombocytopaenia
- Complicated by menorrhagia and bloody mucoid stools
- Send to haematology, who requested ARVs before treating thrombocytopaenia.

Case 1 progress

- Patient started TDF/FTC/EFV
- Initially not very compliant.
- Developed cryptococcal meningitis, sputum smear positive TB.
- Adherence improved, and so did platelet count
- Developed renal impairment ? Due to TDF
- Hb 9.3, Plt 189, CD4 53 and Viral load 654.
- What treatment change would you consider ?

Question slide

- Developed renal impairment ? Due to TDF eGFR 51 ml/min.
- Hb 9.3, Plt 189, CD4 53 and Viral load 654.
- What treatment change would you consider ?

A Continue with current regimen as eGFR> 50

B Change to AZT/3TC/ LPV/r as not suppressed

C Change to ABC/3TC/EFV to preserve kidneys

D stop all ARVs, work her up for renal consult.

Case 1 progress

- Patient seen 6 moths after changing to ABC/3TC/EFV CD4 211, VL <20. Plt 152
- Patient reviewed again 6 months later: **Plt 9**.
- **Admits to having defaulted ARVs after good viral load result. CD4: 52, VL 320000, Plt 9**
- **Question: What went wrong?**

Question slide

- Patient suppressed, rising CD4 (if measured)
- How do you “break the news”?
- A your viral load is undetectable, which means our test cannot find HIV virus in your blood at the moment.
- B our test shows you have successfully suppressed HIV in your blood
- C well done, due to you taking your treatment very well you have suppressed the virus in your blood
- D I can see on your blood tests that you are **really** taking your tablets for HIV, keep on taking them well and you will see the benefits with good health.

Case 1 conclusion

- Patient was admitted with dizziness and bruising, restarted EFV/ABC/3TC.
- Developed ? EFV induced psychosis.
- Started haloperidol and was switched to
- NVP/ABC/3TC
- Currently not psychotic, weaned off haloperidol, on NVP/ABC/3TC
- CD4 :140, VL 70, Plt 162
- Conclusion:

HIV associtated thrombocytopaenia

EFV psychosis, successful switch to NVP

Case 2

- Young male from rural area, sexual debut in 2002 aged 18. Diagnosed with HIV in 2007

d4T/3TC/EFV 2007- 2012 failed

New OI TB meningitis in 2012

Switched to LPV/r/TDF/FTC defaulted in 2013.

Not clear if LPV/r was double dosed during TB Rx.

Returned to care in 2015.

What would you restart him on?

What would you restart him on in 2015?

d4T/3TC/EFV 2007-2012 failed

Switched to LPV/r/TDF/FTC defaulted in 2013.

A same as before defaulting LPV/r/TDF/FTC

B TDF/FTC/EFV as fixed drug combination

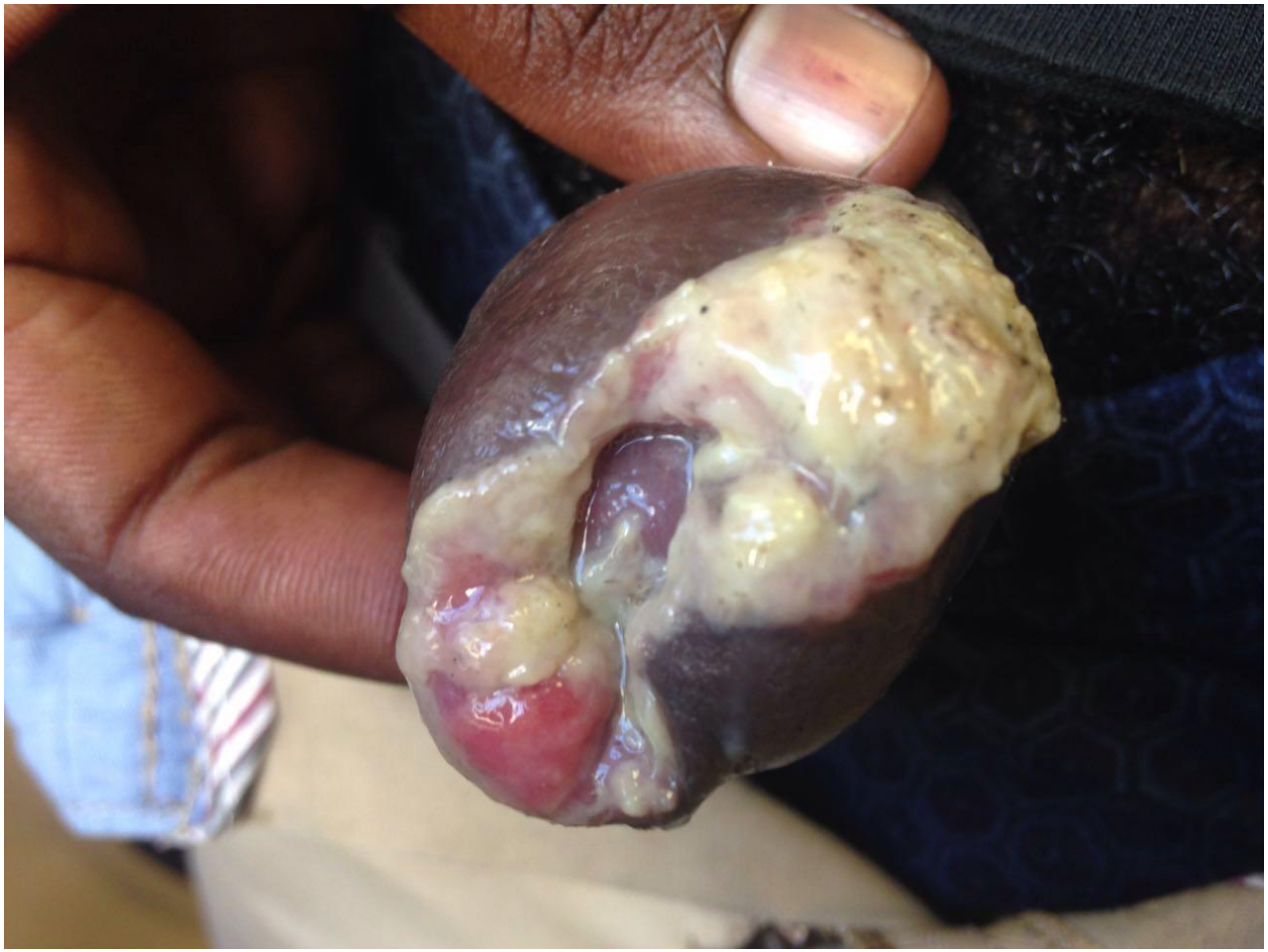
C LPV/r/ABC/3TC as K65R affects ABC less

D atazanavir/ritonavir/TDF/FTC as he might have defaulted to GI side effects - once daily 2nd line

July 2016

- Patient returned to care in 2015 and was started on ABC/3TC/TDF due to LPV/r stockout.
- Not switched back to LPV/r/TDF/FTC until July 2016 when he presented with an oedematous penis with a “necrotic” smell oozing “pus” CD4 54, VL 30200, referred to Infectious diseases clinic in September 2016.

Image of patient’s penis



Question slide

- What do you the most likely diagnosis is?

A squamous cell cancer, superinfected

B superinfected herpes genitalis

C lymphgranuloma venerum

D superinfected syphilitic lesion

HSV type 2 non-healing ulcer

- Patient was admitted, lignocaine penile block .
- Ulcer cleaned and swabbed HSV 2 positive
- Responding to IV acyclovir in 1 g 8 hourly.
- Healed within one week, discharged on acyclovir 400 mg BD po.
- On TDF/FTC/LPV/r from July 2017
- Oct 2016 viral load 380000 copiesl/mL
- Genital ulcer healed.

What would be your approach?

d4T/3TC/EFV 2007-2012 failed

Switched to LPV/r/TDF/FTC defaulted in 2013

Re-initiated in 2015 on TDF/ABC/3TC (LPV/r stockout)

Changed to TDF/FTC/LPV/r in July 2017

3 months viral load not suppressed

A genotype to look for PI resistance

B continue adherence counselling and repeat VL after 6 months.

C change to Atazanavir/ritonavir/AZT/3TC

D repeat viral load in 12 months.

progress

- March 2017
- Viral load repeated: 218000, CD4 10
- Penile ulcer recurrence, not responding to high doses of acyclovir
- HIV Genotype done

PI Major resistance mutations I54V M46I V82A PI

Minor resistance mutations K43T L24I

Protease Inhibitors:

Atazanavir/r (ATV/r) High-level resistance

Darunavir/r (DRV/r) Susceptible

Lopinavir/r (LPV/r) High-level resistance

NRTI resistance mutations K65R K70T

NNRTI resistance mutations H221Y V179F Y181C

Nucleoside RTI:

Abacavir (ABC) High-level resistance

Zidovudine (AZT) Susceptible

Stavudine (D4T) High-level resistance

Emtricitabine (FTC) /Lamivudine (3TC) Intermediate resistance

Tenofovir (TDF) High-level resistance

Non-Nucleoside RTI:

Efavirenz (EFV) Intermediate resistance

Etravirine (ETR) High-level resistance

Nevirapine (NVP) High-level resistance

Rilpivirine (RPV) High-level resistance

3rd line committee response:

The Adult group of the Peer Review Committee for Third Line ART recommended third line agents for this patient.

<u>The recommended regimen is as follows:</u>

- Lamivudine/Zidovudine 150mg/300 mg 12 hourly
- Darunavir 600mg 12 hourly plus Ritonavir 100 mg 12 hourly

conclusion

- Patient commenced 3rd line on 25th August 2017
- Trial of 5% imiquimod (aldara™) cream alternate days
- Awaiting immune reconstitution

Case 3

- 23-years-old, employed lady, diagnosed HIV positive in Jan 2016 CD4 810 (22.8 %)
- ART deferred
- Started TDF/FTV/EFV 23/1/2017 Nadir CD4 280
- Very motivated patient and family
- Height 1.52 m weight 42 kg (BMI 18.1 kg/m^2)
- Started behaving oddly, c/o dizziness and became a messy eater within six weeks of commencement of ARVs.

Case 3 continues..

- Patient became unable to walk unaided by Easter (end of April), had to stop working.
- 31 May taken to a peripheral hospital for LP and work- up. CSF, Electrolytes, TSH, syphilis screen NAD
- End of June 2017 call to ID hotline, patient wheelchair bound extremly atactic, no nystagmus, inappropriate in affect, calls a soft toy her baby, disorientated to time and place, deteriorating in daily functioning, family worried.
- Could we to CT at King Edward VIII Hospital?

Question: What did the CT show?

A cerebellar tumour, most likely non-benign

B brain atrophy, marked frontal lobe atrophy

C CT normal

D cysts and scolices, mild oedema in keeping with neurocysticercosis

Normal CT brain

- CSF
- **CSF Analysis:**
  Cell Count:
  Polymorphs 0 /uL
  Lymphocytes 0 /uL
  Erythrocytes 0 /uL
  Unidentified cells 0 /uL
- CSF glucose 3.8 mmol/L, serum glucose: 5.5 mmol/L
  CSF protein 0.31 g/L 0.15 - 0.45
- HZV, CMV, JC virus, VRDL, CrAG, GXP, TB cult all negative

Q: What could be the problem?

A EFV toxicity

B HIV dementia

C Manic defence reaction due to unresolved childhood trauma

D schizophrenic episode

Efavirenz toxicity

- Efavirenz has been linked to early (two to six weeks) transient as well as late neuropsychiatric effects, catatonia, psychosis and ataxia.
- All of these have been directly linked to EFV toxicity.
- The risk for toxicity has been associated with loss of function polymorphisms of cytochrome 2B6, the main metabolising enzyme for EFV.
- It is estimated that about 20% of sub-Saharan Africans are genetically slow metabolisers and may be at risk of EFV toxicity.
- Weight is another factor that predisposes a patient to EFV toxicity, patients weighing less than 40 kg should be prescribed a reduced dose of 400 mg

- DHEDA, M. Efavirenz and neuropsychiatric effects. **Southern African Journal of HIV Medicine**, 18, Apr. 2017. Available at: <http://www.sajhivmed.org.za/index.php/hivmed/article/view/741/938>

Drug levels

Dear Clinicians and Medical Staff

Please be advised: we are offering therapeutic drug monitoring for antiretroviral drugs at CMJAH. The list of ARV that can be measured are as follows:

Atazanavir	Tenofovir
Lopinavir	Zidovudine
Ritonavir	Efavirenz
Emtricitabine	Nevirapine
Lamivudine	Dolutegravir

The test code on TRAK is **ARVDL**

REQUIREMENTS:
Plasma from an EDTA sample (purple top tube) is required for the analysis of ARV drug levels.
The sample needs to be collected at trough level i.e. prior to the administration of the next dose.
If sample deliver will take longer than 24 hours, the sample should be centrifuged at 3500rpm for10min, the plasma separated and sent at 4°C in a polypropylene tube with the orginal EDTA attached .
For more information please contact the laboratory on 011 4898448.

Case 3 conclusion

- ARVs stopped 27 June 2017
- Inpatient treatment with haloperidol and disipal (orphenadrine) for pschycosis and extra-pyramidal symptoms (psychiatry).
- Patient was discharged after >14 days off all medication with definite improvement
- Started NVP/3TC/TDF on 14 Aug 2017 CD4 775
- LFT ok after 2 weeks.

Case 4

- Patient SM 31 yrs old female diagnosed HIV + in 2000. Fell pregnant in 2004 and started D4T/3TC/NVP in April ‘04 baseline VL 390000
- CD4 352, VL 1100 in March 2005
- CD4 340, VL <25 Nov 2006
- CD4 329, VL <25 July 2007
- CD4 274, VL 7500 Feb 2008
- Complaining about vomiting and abdominal pain
- What to do next?

Viral load unsuppressed on 1st line Question

- What to do next?

A increase adherence counselling, do pill count

B repeat viral load after 2 months

C send for further investigations like U/S Abd

D all of the above

Case 4 progress

- Adherence counselling done, pillcount over 2 months ok, VL repeated after 2 months
- CD4 202 VL 3300 (previous CD4 274, VL 7500 Feb 2008)
- U/S abdomen NAD, Lactate level normal, UE/FBC normal, PTB in 1994, no other OIs, shack dweller with 2 daughters aged 12 & 3 yrs
- Still on/off nausea/vomiting/ abdominal pain
- Changed to AZT/DDI/LPV/r in May 2008
- CD4 234, VL 41000 at change.

Progress July 2008

- Patient not taking ARVs correctly. Takes all on empty stomach not first the ddI and then 1 hour later LPV/r and AZT with food.
- Still complaining of GI symptoms
- Upper scope: oesophageal candidiasis (fluconazole given)
- October 2008 (5/12 into SLART) CD4 165, VL 11000
- C/O painful feet with numbness, ongoing GI symptoms with vomiting.
- Plan: Repeat CD4/VL in 4 months, add gabapentin (neurontin™) added for neuropathic pain add 3TC to strengthen regimen.

Genotype available through study

D4T/3TC/NVP April 2004 to May 2008 failed

Changed to AZT/DDI/LPV/r in May 2008 3TC added

March 2009 CD4 155, VL 11000

What do you expect the genotype to show?

VL at genotype 58000 May 2009

- A NRTI mutations and NNRTI mutations
- B PI mutations
- C All of the above
- D None of the above - wildtype

Genotype wildtype despite 5 years ARVs

- Patient was counselled and kept on 2nd line.
- Dissappeared for 2 years…
- … “re”-initiated at local clinic on d4T/3TC/NVP
- “Re”-referred with failure in July 2011
- CD4: 155 VL 58000 at disappearance on reg 2
- March 2010: CD4: 238 VL 535 back on reg 1
- March 2011: CD4: 351 VL 713 on reg 1
- May 2011 CD4: 291 VL 1751 failing reg 1
- July 2011 changed to LPV/r/TDF/3TC
- Aug 2011 pat c/o bitter taste in mouth, bloating
- Sept 2011 CD4 327 VL <150 now also vomiting and diarrhoea

Q: What would you do?

GI side effects to LPV/r/TDF/3TC for 2 months

A counselling to adhere despite side-effects

B supportive treatment with maxalon and lomotil

C All of the above

D switch to ATV/r (boosted atazanvir)/3TC/TDF

progress

- LPV/r/TDF/3TC continued supportive meds and reassurance that side effects would improve
- 4 moths later, weight loss of 2 kg since switch, still GE side effects, switched to atazanavir/r
- 2 moths later: tinge of jaundice noted by doctor
- 3 months on ATV/r/3TC/TDF deeply jaundiced
- No vomiting/diarrhoea
- Total Bili 129 µmol/L (N=5-21), conjug. Bili 3 µmol/L

  ALT, ALP, GGT normal

What is the likely cause for elevated Bili?

- A obstructive jaundice due to gall stones
- B pancreas head CA compressing bile duct
- C herbal medication use by patient
- D drug side effect

Atazanavir induced jaundice

- ATV is associated with unconjugated hyperbilirubinaemia in 6-40% of patients,
- overt jaundice in 7-8% and
- discontinuation in up to 2%.
- The pathophysiology of ATV-hyperbilirubinaemia is analogous to Gilbert's syndrome; ATV competitively inhibits UDP-glucuronyltransferase (UGT) enzymes leading to reduced glucuronidation of bilirubin and increased levels of unconjugated bilirubin.
- Patients with the UGT1A1*28 genotype are particularly, but not exclusively, vulnerable

Case 4 Conclusion

- ATV/r/3TC/TDF (initiated November 2011)
- Transient severe hyperbilrubinaemia,
- persisting mild hyperbilirubinaemia
- May 2013 psychotic episode: voices telling her to stab her nine-year-old daughter
- 2 psychiatric stays until successfully placed on Sodium Valproate, risperdone and lorazepam
- (weight gain : 30 kg ? Epilim side effect
- CD4: 452 (Feb 2017) VL below limit of detection since 2011
- Schizophrenia prevalence worldwide around 2-10/ 1000

- MiyaokaT, Seno H et al The Journal of Clinical Psychiatry [01 Nov 2000, 61(11):868-871] Schizophrenia-associated idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). (PMID:11105741)

Case 5 adolescent case

- In memoriam A. M. - rest in peace!
- Baby boy born in 1998 to HIV negative parents
- Both parents employed, infant cared for in Crèche and by relatives
- “Rape” incident in 2000
- Diagnosed HIV+ aged 8 in 2006 CD4 9%
- Started d4T/3TC/EFV weight 28 kg

Child's progress

- Different care givers …
- CD4 20 % VL 225 (June 2007) weight 31 kg
- Never fully suppressed.. Failed reg 1 by 2011
- T/f to Paed ID adolescent care aged 13 yrs, disclosed
- Changed to ABC/3TC/Kaletra in July 2011
- By September 2013 (age 15) failing VL high, weight 18 kg
- Chronic GE, isospora belli on stool and duodenal biopsy
- Diagnosed with TB, send to inpatient TB facility for 6 months, HOPEFULLY LPV/r double dosed??
- TB cured, discharge weight 30 kg, height 1.44 m (severely stunted) VL 38550

Q: What would you do?

- A Genotype
- B counsel care-give and child
- Repeat VL in 3 months time
- Refer to adult ID (age now 16)

Genotype

- Current regimen: LPV/r/ABC/3TC
- NO PI mutations
- NRTI M184V, K219R
- NNRTI K103N

- Resistant to ABC, 3TC, EFV, NVP
- Treatment adjusted to AZT/3TC/ATV/r
- Transferred to adult ID care

Patient doing ok,

- CD4 121, VL 137 (Dec 2016)
- But… coughing, losing weight: 25 kg
- GXP +, Rif sensitive

Q What do you do?

A start rifafour (RZHE)

B start rifafour and streptomycin for retreatment

C change to ATV/r to 2x LPV/r and start rifafour

D cont ATV/r, give rifabutin, PZA, Ethambutol and INH

Conclusion case 5

- Started rifabutin, and other individual TB drugs (10 extra tablets) with ATV/r/AZT/3TC
- Recurrence of chronic GE, in/out of hospital
- Always dehydrated, acidotic with low K^+
- High dose Bactrim and ciprofloxacin used
- Some admissions line sepsis with MRSA
- Patient deteriorated and died in hospital in March 2017 aged 18 years and 7 months.

The END

- Thank you for your participation and discussion

- Acknowledgement to:
- Prof MYS Moosa for years of mentoring
- Patients and staff at King Edward VIII Hospital

- “ you always learn something new”