Difference of opinion?

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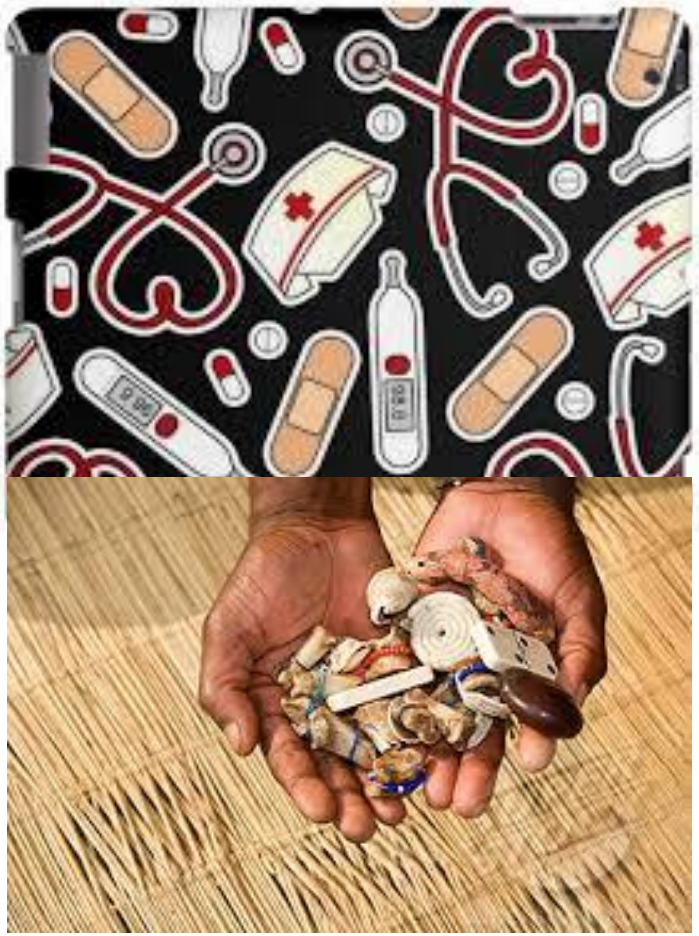
24 Sep 2014

Meet NN

- 52 years, female
- Nurse in pre-ART clinic
- Referred Feb 2012 by dermatologist
- History of severe reactions to ART
- Erythema and bullous eruptions after Atripla started



The most likely cause is

A. Lamivudine (3TC)
B. Efavirenz (EFV)
C. Emtricitabine (FTC)
D. Tenofovir (TDF)

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History

- HIV infection diagnosed 2004 (last negative test 1999 ANC)
  - Latest CD4 = 185 cells/mm^3 (Dec 2011)
- Depression 2000; no other chronic diseases
- Recently came off fluoxetine
- Currently taking prednisone and chlorpheniramine from dermatologist
- Allergies: possibly cotrimoxazole

ARV history

When?	Regimen	Duration	Reason for stopping
2004	d4T + 3TC + NVP	5 days	Severe rash
2009	d4T + 3TC + NVP	2 days	Erythema multiforme, Stevens-Johnson syndrome (SJS)
Jan 2012	TDF + FTC + EFV (FDC)	2 days	Erythema multiforme and bullous eruptions (referred to dermatologist)

- Examination unremarkable
  - Occasional small soft mobile lymph nodes
  - Rash: resolving lesions, no mucosal involvement or secondary infection
- Fur bracelet right wrist; similar object around waist

Next visit: June 2012

- Despite frequent follow up calls to return for counselling and to restart ARVs (low CD4)
  - Scared about restarting meds after previous severe reactions
- On return, NN was well; no TB symptoms
- Felt ready to restart ARVs
- Medical aid required laboratory tests
  - CD4 count = 74 cells/mm^3
  - VL = 148 133 copies/mL

What ARVs would you choose?

A. TDF + FTC/3TC + EFV
B. AZT + 3TC + LPV/r
C. TDF + FTC + ATV/r
D. ABC + 3TC + EFV

What we chose

- TDF + FTC + ATV/r started 10 Aug 2012
- Developed rash and fatigue within 24 hours of first dose
  - Stopped ARVs
- Also had cough for 3 weeks and LOW
  - AFBs at clinic: smear negative
- No other systemic or constitutional symptoms
- Rash: target lesions and blisters (limbs > trunk), no mucosal involvement; apyrexial
- Rest of examination unremarkable – no signs TB

What did we do?

- Laboratory tests
  - FBC and UECr normal/NCS
  - Mild elevation liver enzymes (ALT > AST)
  - CD4 99 cells/mm^3
  - TB cultures: negative
- CXR: normal

What did we do?

- Antibiotic for cough and antihistamine for itch
- Contacted MA HIV programme to discuss
- Told to restart same regimen and treat through:
  - Rationale: rash is IRIS
  - Asked to speak to medical advisor: denied
- Rash due to 3TC/FTC hypersensitivity?

What do you think?

A. IRIS
B. Hypersensitivity reaction
C. Cotrimoxazole allergy
D. None of the above

NN made decision herself

- Restarted regimen of her own accord: rash within 12 hours of first dose
  - Erythematous and target lesions and blisters
  - More extensive and extremely itchy
  - Eyes red and gritty; no other mucosal involvement
  - Mild aches and felt warm
- Cough now resolved and weight stable; no night sweats
- ARVs stopped immediately

Which statement is true?

A. NSAIDs can cause SJS/TEN
B. Nevirapine is the ARV most commonly associated with SJS/TEN
C. 3TC and FTC can cause SJS/TEN in just under 1% of patients
D. All of the above

Which statement is true?

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What next?

- A lot of to and fro with MA HIV programme
  - IRIS versus drug hypersensitivity
- Agreed to disagree, but managed to agree a treatment plan:
  - LPV/r monotherapy for one month
  - Add in backbone containing neither 3TC/FTC, ie ddI and ZDV (Aug 2012)
- NN very anxious – counselled extensively
- Eventually returned Oct 2012 (!) to recommence

NN started monotherapy

- Commenced LPV/r monotherapy 18 Oct 2012
  - Called daily to ask about SEs
  - 24 Oct: no rash; felt well
- Continued LPV/r monotherapy for one month
  - Only complained of mild GI effects
- After one month, added ddI and ZDV
  - No rash or other symptoms (“Doc, I feel great, I owe you my life”)

Next visit Jan 2013

- Doing well: tolerating ART and no TB symptoms
- Due for monitoring tests
  - CD4 count = 222 cells/mm^3; VL = 127 copies/mL
  - FBC: raised MCV
- IPT commenced one month previously (by NIMART nurses at PHC where she worked)

Next monitoring visit June 2013

- Numbness of the finger tips for 2-3 months, L > R
- Otherwise well: no self reported adherence problems; tolerating regimen well
- Neuro examination confirmed peripheral neuropathy (bilateral, upper and lower limbs)
- Laboratory tests:
  - CD4 count = 214 cells/mm^3; VL = 63 copies/mL

Which drug can cause PN?

A. Isoniazid
B. ddI
C. AZT
D. Any of the above

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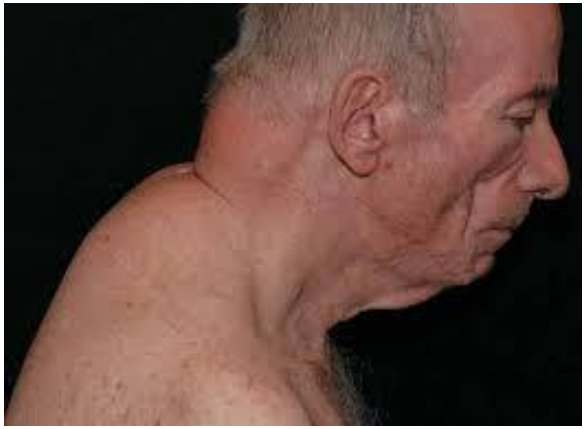
Next monitoring visit Dec 2013

- Progression of the PN
- Body changes: facial and limb wasting
- Laboratory tests:
  - CD4 count = 230 cells/mm^3; VL <40 copies/mL
- Requested change of regimen due to pill burden, and side effects
  - Stigma of lipodystrophy
  - PN progression affecting work



Which ARV can cause lipodystrophy?

A. ddI
B. d4T
C. ZDV
D. All ARVs have been associated with lipodystrophy

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So I mustered up my alter ego….

… preparing to do battle with HIV programme medical advisors again

- Changed NN's regimen:

  LPV/r + RAL
- Started in Mar 2014
- Well tolerated
- Due for monitoring tests

IRIS

- Pathological inflammatory response after ART started caused by recovering immune system

- 2 main types of infective forms
  - Unmasking: untreated infection (CM; TB)
  - Paradoxical: patient on treatment (TB)

- Other types: auto-immune; malignancies; other inflammatory conditions

IRIS

Unmasking	Paradoxical
• Infection untreated when ART initiated • Presents with **atypical** or accelerated presentation on ART – Eg localised inflammation in typically disseminated disease	• On treatment for infection when ART started and improving • Return of clinical manifestations • TB: 1-4 weeks (within 3 months); 8-45%

Alternative explanations for deterioration

No diagnostic test	Common forms of IRIS in SA

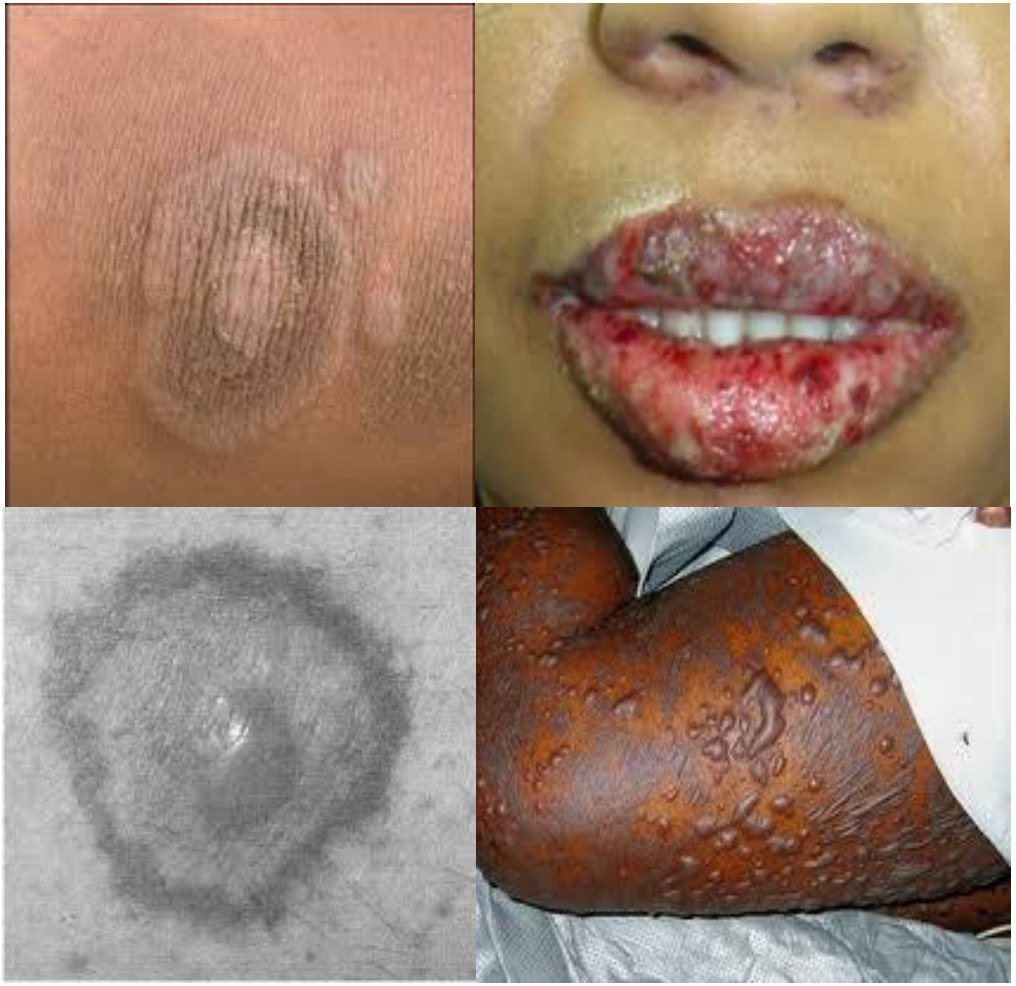
• Failure of (TB) treatment
  – Poor adherence
  – TB drug resistance
• Different OI or malignancy
• Drug toxicity or reaction
	• TB
	• Cryptococcus
	• Acne
	• Molluscum contagiosum
	• HSV and zoster
	• Hepatitis B
	• CMV
	• Kaposi's sarcoma

Hypersensitivity

- HIV infected patients higher incidence rashes
  - TH2/TH1 imbalance
  - Polypharmacy
  - Altered drug metabolism
- NNRTIs most commonly associated with skin rashes (especially NVP)
- Typically initial reaction within approx one week of exposure; subsequent exposure 1-2 days
- ABC hypersensitivity: never rechallenge

Drugs to consider

- ARVs
- TB drugs
- Cotrimoxazole
- Dapsone
- Anticonvulsants
- Minocycline
- NSAIDs



Lessons learned

- HIV management programmes provide excellent guidance, especially for doctors without much HIV management experience
- The clinical judgement of the doctor who is managing a patient should be considered
- Patient is in front of the doctor
- Patient trusts them or would go elsewhere
- Sometimes you have to be willing to fight for what you believe is best for your patient

Thank you

- NN for consenting to have her case presented
- Audience for participating
- SA HIV Clinicians Society for invitation to present this case