Difference of opinion?

Michelle Moorhouse
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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A. Lamivudine (3TC)
B. Efavirenz (EFV)
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D. Tenofovir (TDF)
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

<table>
<thead>
<tr>
<th>When?</th>
<th>Regimen</th>
<th>Duration</th>
<th>Reason for stopping</th>
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<tbody>
<tr>
<td>2004</td>
<td>d4T + 3TC + NVP</td>
<td>5 days</td>
<td>Severe rash</td>
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<tr>
<td>2009</td>
<td>d4T + 3TC + NVP</td>
<td>2 days</td>
<td>Erythema multiforme, Stevens-Johnson syndrome (SJS)</td>
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<tr>
<td>Jan 2012</td>
<td>TDF + FTC + EFV (FDC)</td>
<td>2 days</td>
<td>Erythema multiforme and bullous eruptions (referred to dermatologist)</td>
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- 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/mm³
  – 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?

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
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
Which drug can cause PN?

A. Isoniazid
B. ddI
C. AZT
D. Any of the above
Next monitoring visit Dec 2013

• Progression of the PN
• Body changes: facial and limb wasting
• Laboratory tests:
  – CD4 count = 230 cells/mm³; 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
Which ARV can cause lipodystrophy?

A. ddi
B. d4T
C. ZDV
D. All ARVs have been associated with lipodystrophy
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
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<th><strong>Paradoxical</strong></th>
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<td>• Infection untreated when ART initiated</td>
<td>• On treatment for infection when ART started and improving</td>
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<td>• Presents with <em>atypical</em> or accelerated presentation on ART</td>
<td>• Return of clinical manifestations</td>
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<td>- Eg localised inflammation in typically disseminated disease</td>
<td>• TB: 1-4 weeks (within 3 months); 8-45%</td>
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### Alternative explanations for deterioration

**No diagnostic test**

- Failure of (TB) treatment
  - Poor adherence
  - TB drug resistance
- Different OI or malignancy
- Drug toxicity or reaction

**Common forms of IRIS in SA**

- 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