Clinical skills building - HIV drug resistance

Richard Lessells
Clinical case

44-year old HIV-positive male
HIV diagnosis 2010
Pre-treatment CD4+ count not known

Initiated first-line ART (TDF/FTC/EFV) in private sector 2010 –
transferred into public sector Oct 2011

4 x episodes pulmonary TB (last 2010)
Clinical chart

PTB  Virological failure  Genotype

CD4 (cells/ul)  VL (copies/ml)


EFV  FTC  3TC  LPV/r  TDF  AZT

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## Genotypic resistance test report

**Antiretroviral experience:** TDF, FTC, EFV, AZT, 3TC, LPVr  
**Subtype:** HIV-1 Subtype C  
**Resistance interpretations:** HIVdb 8.6

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutations</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>M184V, T215S</td>
<td>Potential low-level resistance</td>
<td>10</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>M184V</td>
<td>High-level resistance</td>
<td>60</td>
</tr>
<tr>
<td>Abacavir</td>
<td>M184V, T215S</td>
<td>Low-level resistance</td>
<td>20</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>M184V</td>
<td>High-level resistance</td>
<td>60</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>M184V, T215S</td>
<td>Susceptible</td>
<td>-5</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>-</td>
<td>Susceptible</td>
<td>0</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>-</td>
<td>Susceptible</td>
<td>0</td>
</tr>
<tr>
<td>Etravirine</td>
<td>-</td>
<td>Susceptible</td>
<td>0</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>-</td>
<td>Susceptible</td>
<td>0</td>
</tr>
<tr>
<td>Atazanavir/r</td>
<td>-</td>
<td>Susceptible</td>
<td>0</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>-</td>
<td>Susceptible</td>
<td>0</td>
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</table>
Question

Does the genotypic resistance test help you to understand this man’s ART adherence?

A. Yes - he must be completely non-adherent to ART

B. Yes - he must have differential adherence, i.e. he is taking AZT/3TC but not LPVr

C. Yes – he must have poor adherence but difficult to say more than that

D. No - it doesn’t help at all
Routine genotypic resistance test data
NHLS, KwaZulu-Natal, 2015-16

• All genotypic resistance tests performed for adult second-line ART failure 2015-16 (N = 353)

• Median age 34 yrs (IQR 19-42)
• 59% female
• 93% LPVr-based regimens

• Median duration second-line ART 30 months (IQR 18-48)
• Median duration all ART 72 months (IQR 50-95)
Question

In KwaZulu-Natal 2015-2016, approximately what proportion of adults with a resistance test done for virological failure on second-line ART had at least one major PI mutation?

A. 10%
B. 20%
C. 33%
D. 50%
E. 75%
Routine HIV drug resistance testing
NHLS, KwaZulu-Natal, 2015-2016

33% at least one major protease mutation

So the majority were failing without protease resistance

66% NRTI mutations
64% NNRTI mutations

19% no drug resistance mutations
PI resistance at second-line ART failure
Meta-analysis of 13 studies from sub-Saharan Africa

At a cohort level, proportion with major PI mutations is closely associated with median time on second-line ART

Stockdale CID 2018
Why do most adults with virological failure on second-line ART have no major PI mutations?

The development of protease inhibitor resistance is relatively uncommon at all adherence levels.

Viral fitness of resistant virus

Genetic barrier to resistance

Potency
Why do most adults with virological failure on second-line ART have no major PI mutations?
Why do most adults with virological failure on second-line ART have no major PI mutations?

Association between adherence and drug resistance quite different for PIs compared to NNRTIs

Rosenbloom Nature Med 2012
Clinical chart

- CD4 (cells/μl)
- VL (copies/ml)

- 1/2010: EFV, FTC, 3TC, LPV/r, TDF, AZT
- 7/2011: PTB
- 1/2013: Virological failure
- 7/2014: Genotype
- 1/2016: PTB (Xpert +)
- 7/2017: PTB (Xpert +)

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Question

When would you repeat a resistance test in an adult patient who has no major PI mutations, continues on second-line ART and has persistent viraemia despite enhanced adherence counselling?

A. After 3 months if VL > 1000 copies/mL
B. After 3 months if <1 log_{10} copies/mL decrease in VL
C. After 6 months if VL > 1000 copies/mL
D. After at least 12 months if persistent VL > 1000 copies/mL
E. When immunological or clinical failure develops
Clinical chart
# Genotypic resistance test report

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<td>Intermediate resistance</td>
<td>55</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>M41L, M184V, T215S</td>
<td>High-level resistance</td>
<td>65</td>
</tr>
<tr>
<td>Abacavir</td>
<td>M41L, M184V, T215S</td>
<td>Intermediate resistance</td>
<td>45</td>
</tr>
<tr>
<td>Emtricitabine</td>
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<td>15</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>A98G</td>
<td>Intermediate resistance</td>
<td>30</td>
</tr>
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<td>L10F, M46I, I54V, V82A</td>
<td>High-level resistance</td>
<td>80</td>
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Protease mutations

Major PI mutations – mutations occurring within the active binding site of protease enzyme which disrupt PI binding; have the greatest impact on PI susceptibility

Minor PI mutations – mutations outside the active binding site; can enhance resistance and can be compensatory, i.e. restore enzyme activity or reverse viral fitness defects
Third-line ART algorithm

- PI score ≥15
  - DRV/r
    - + 3TC or FTC
    - + AZT or TDF
  - and
    - TDF/AZT ≥30
    - or
    - DRV/r ≥15
    - and
    - TDF/AZT ≥30
    - and
    - DRV/r ≥15
    - and
    - ETR <30
  - Add RAL/DTG
  - Add ETR

- DRV/r
  - FTC
  - TDF
Case progress

Admitted to hospital while waiting for third-line ART
Treated for chest infection & gastroenteritis (antibiotics, fluids)
Sputum Xpert Ultra negative
Attends clinic one week post-discharge to start third-line ART
Case progress

Admitted to hospital while waiting for third-line ART
Treated for chest infection & gastroenteritis (antibiotics, fluids)
Sputum Xpert Ultra negative
Attends clinic one week post-discharge to start third-line ART

Blood chemistry:
- Sodium: 132 mmol/L
- Potassium: 3.8 mmol/L
- Chloride: 103 mmol/L
- Bicarbonate: 20 mmol/L
- Anion gap: 13 mmol/L
- Urea: 8.6 mmol/L

Creatinine and estimated GFR:
- Creatinine: 120 umol/L
- eGFR (MDRD formula): 57 mL/min/1.73 m²

Liver function tests:
- Total protein: 79 g/L
- Albumin: 31 g/L
- Total bilirubin: 8 umol/L
- Alanine transaminase (ALT): 144 U/L
- Alkaline phosphatase (ALP): 267 U/L
- Gamma-glutamyl transferase (GGT): 259 U/L

Calculated CrCl 61 mL/min
Question

What would you do now?

A. Start recommended third-line ART regimen (TDF/FTC/DRV/r) immediately
B. Start modified third-line ART regimen (ABC/3TC/DRV/r) immediately
C. Re-admit to hospital for further investigation
D. Review in one week with repeat U&Es, LFTs
E. Phone local ID specialist for advice
Case progress

Admitted to hospital while waiting for third-line ART
Treated for chest infection & gastroenteritis (antibiotics, fluids)
Sputum Xpert Ultra negative
Attends clinic one week post-discharge to start third-line ART

Repeat U&Es, LFTs one week later

**Blood chemistry:**
- Sodium 134 L mmol/L
- Potassium 3.5 mmol/L
- Chloride 101 mmol/L
- Bicarbonate 25 mmol/L
- Anion gap 12 mmol/L
- Urea 8.2 H mmol/L

**Creatinine and estimated GFR:**
- Creatinine 100 umol/L
- eGFR (MDRD formula) >60 mL/min/1.73 m²

**Liver function tests:**
- Albumin 31 L g/L
- Total bilirubin 10 umol/L
- Alanine transaminase (ALT) 24 U/L
- Alkaline phosphatase (ALP) 112 U/L
- Gamma-glutamyl transferase (GGT) 128 H U/L
Key learning points

- Most adults with virological failure on second-line ART do not have major PI mutations

- Adherence measurement, support and interventions remain critical to prevent development of drug resistance

- Genotypic resistance testing should be repeated in people with persistent viraemia despite good adherence on second-line ART, but optimal timing not clear

- Once PI resistance occurs, most have high-level LPVr resistance and at least low-level DRV/r resistance