Resistance testing for Third Line

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Third-line ART

- Third-line ART is used when a patient has experienced virological failure on drugs from the NRTI, NNRTI and PI classes (with documented PI resistance).
- Adherence interventions should be intensified.
When to Use Resistance Testing

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<tbody>
<tr>
<td>Primary/acute</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
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<tr>
<td>Postexposure prophylaxis</td>
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<tr>
<td>Chronic, Rx naive</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
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<tr>
<td>Failure</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
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<tr>
<td>Pregnancy</td>
<td>Recommend</td>
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<tr>
<td>Pediatric</td>
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*Test source patient especially if treated with antiretroviral drugs.

### Failure of a boosted PI-based regimen

| Adults and children with two VL measurements >1000 RNA copies/ml and/or a <2 log₁₀ drop in VL while on PI-based ART (measurements 3-6 months apart) | Recommended | Failure on PI regimens is almost always due to poor adherence. Adherence issues should be addressed comprehensively between the 2 measurements. Resistance testing should be performed while the patient is on the failing regimen or within 4 weeks of discontinuation. |
What information can we get?

- Resistance tests serve two purposes:
  - Adherence test.
  - If resistance mutations are present, ability to chose a regimen.
What information can we not get?

- NRTI mutations that are present only represent the current regimen.
  - Presume all first generations will not work

- NNRTI mutation are usually archived
Requirements for resistance testing

• Patient must be on ART at the time or stopped within the last 4 weeks.
• Should not be done on the first detectable viral load
• No rush – between 3-6 months.
Measures of adherence

• Self-reported, short-term adherence
• Dispensing-based long-term adherence
• Consistency of visit attendance
• Pill count-based medium-term adherence
• Electronic cap monitoring
Adherence support

- Inadequate treatment literacy
- Side effects
- Depression and other mental illnesses
- Poverty and food insecurity
- Work related issues
- Substance use
- Social problems
- Denial
- Pill burden
- Altered fertility intentions
- Conflict of opinions
Principles

- First-generation NNRTIs have no place in third-line therapy
- A boosted PI with the broadest resistance profile should be selected
- No double ritonavir-boosted PIs.
- The addition of 3TC (or FTC) is recommended
- Consideration of the addition of other salvage drugs (e.g. RAL and/or ETV) will depend on genotype resistance test result
Patients who return after defaulting therapy

- Restart the same regimen and repeat HIV viral load measurements after 3 months
- Switching to a second-line regimen should be considered if the viral load is not suppressed at this point.
- AZT could be substituted for D4T.
- Do not substitute TDF
Is VL < 50 copies/mL Achievable in Tx-Experienced Patients With MDR HIV?

- Assess ability to adhere to future treatment options
- Thorough assessment of current and past resistance
- Tropism assessment
- Treatment history
- Available active agents
  - Preferably ≥ 2 fully active agents needed
  - Except in extraordinary circumstances, adding only 1 drug should be avoided

• Consider emerging treatment options and need for immediate enhancement of current regimen (ie, risk of clinical progression)
Total patients: n=69
- Ineligible: Follow-up <3 months: n=20
- Viral load missing: n=2

Study population: n=47
- Secondary outcomes:
  - RIP: n=1
  - LTF: n=1
  - TFO: n=1

Primary outcomes: n=44
- Suppressed at VL1: n=18
  - TFO: n=1
  - LTF: n=1
  - RIP: n=2
- Not suppressed after VL1: n=21
- Suppressed at VL2: n=7
- Not suppressed at VL2: n=10
- Suppressed at VL3: n=2
- Not Suppressed at VL3: n=7
- LTF: n=1

Genotypes: n=4
- Not resistant, Unsuppressed

Known adherence issues: n=2
- VL<1000: n=1
- Not started 3rd line: n=2
- Genotypes: n=4
- Not resistant, Unsuppressed

Started 3rd line: n=3
- Not started 3rd line: n=2
- Suppressed at VL1: n=3

Known adherence issues: n=2
- VL<1000: n=1

Not suppressed at VL1: n=21
• All effort should be made to address adherence problems
• “understand the failure”
• Once adherence problems are solved, resuppresion if often possible under the same treatment.
• Request a Hep B sAg for patients failing a TDF base regimen. If Hepatitis B is positive, TDF should be included in the new regimen. (TDF is active against Hepatitis B virus)
Background:

- First-line ART for children < 3 years, PI + NRTI
- Children failing ritonavir or ritonavir-boosted lopinavir (LPV/r)
- Major PI resistance mutations (MPIRM)
PROTEASE INHIBITOR RESISTANCE IN SOUTH AFRICAN CHILDREN WITH VIROLOGIC FAILURE

Materials and Methods: Pediatric HIV patients at Tygerberg Academic Hospital with virologic failure on a PI regimen.

Results: MPIRM were found in
12 of 17 patients exposed to RTV-sPI
1 of 13 patients treated with LPV/r.

• Conclusions: RTV-sPI in infants and children poses a significant risk of MPIRM

• van Zyl, G.U. et al., 2009
### TABLE 1. Main Characteristics of Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>LPV/r (n = 13)</th>
<th>RTV-sPI (n = 8)</th>
<th>RTV-sPI Followed by LPV/r (n = 9)</th>
<th>Total (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first study visit (mo)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
<td>27</td>
<td>20</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Range</td>
<td>11–65</td>
<td>6–91</td>
<td>26–53</td>
<td>6–91</td>
</tr>
<tr>
<td>MPIRM (%)</td>
<td>1 (8%)</td>
<td>7 (88%)</td>
<td>5 (55%)</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Concurrent TB therapy (number %)</td>
<td>5 (38%)</td>
<td>7 (88%)</td>
<td>7 (78%)</td>
<td>19 (63%)</td>
</tr>
</tbody>
</table>

LPV/r indicates Lopinavir co-formulated with low-dose ritonavir; RTV-sPI, RTV as single protease inhibitor; MPIRM, major protease inhibitor resistance mutations; TB, *Mycobacterium tuberculosis*.
• van Zyl, G.U. et al., 2009

- Resistance rates and patterns among children in developing countries in whom antiretroviral treatment has failed.
- Outcomes in 3241 children were eligible.

- Sigaloff KC et al 2011

- Viruses with resistance-associated mutations were isolated from 90% (95% CI 88-93%) of children.

- The prevalence of mutations associated with
  - NRTI - 80%,
  - NNRTI - 88%
  - PI- 54%.
Protease Inhibitor Resistance Is Uncommon in HIV-1 Subtype C Infected Patients on Failing Second-Line Lopinavir/r-Containing Antiretroviral Therapy in South Africa

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (inter quartile range)</th>
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<tbody>
<tr>
<td></td>
<td>No PI major mutations (n = 70)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34 (29–40)</td>
</tr>
<tr>
<td>CD4+ T-cells/mm³</td>
<td>141 (75–245)</td>
</tr>
<tr>
<td>HIV-1 RNA (copies/mL)</td>
<td>184,779 (8790–166,300)</td>
</tr>
<tr>
<td>Time on second-line (months)</td>
<td>16 (7–18)</td>
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</table>

- Wallis, C.L. et al., 2011.
<table>
<thead>
<tr>
<th>Resistance Mutations</th>
<th>n (%)</th>
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<tbody>
<tr>
<td><strong>NRTI mutations</strong></td>
<td></td>
</tr>
<tr>
<td>M184V</td>
<td>15 (20%)</td>
</tr>
<tr>
<td>K65R</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Q151M</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>TAMs</td>
<td>10 (13%)</td>
</tr>
<tr>
<td><strong>NNRTI mutations</strong></td>
<td>39 (52%)</td>
</tr>
<tr>
<td>K103N</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>V106M</td>
<td>9 (12%)</td>
</tr>
<tr>
<td><strong>Any PR mutations (major and minor)</strong></td>
<td>67 (89%)</td>
</tr>
<tr>
<td><strong>Major LPV mutations</strong></td>
<td></td>
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<tr>
<td>M46I, L76V</td>
<td>1</td>
</tr>
<tr>
<td>M46I</td>
<td>1</td>
</tr>
<tr>
<td>L33F, I54S, V82A, I84V</td>
<td>1</td>
</tr>
<tr>
<td>L33F, M46I, I54V, I84V, L90M</td>
<td>1</td>
</tr>
<tr>
<td>M46I, I54V, L76V</td>
<td>1</td>
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</tbody>
</table>
• Major lopinavir resistance mutations were infrequent (5 of 75; 7%), indicating that drug resistance is not the main barrier to future viral suppression.