Viral load elevation and virologic failure in children/adolescents: A practical approach

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Background

- Viral load is the most accurate measure of treatment success
- Viral load elevation = > 50 cps/ml
- Blip = 50-<1000 cps/ml
- Virologic failure = 2X VL > 1000 cps/ml
- Virologic failure occurs in about 20% of children on ART by 3 years on treatment
- In adolescents these numbers are much higher: 50% less likely to be adherent and 70-75% less likely to have VL <400cps/ml

Patten/Fairlie, *Pediatric workshop* 2016; *IWHOD* 2017; Davies, *JAIDS* 2011; Nachega, *JAIDS* 2009
National ART regimens: 1\textsuperscript{st} line

- ABC and 3TC
- LPV/rtv:
  - <3yr/10kg
- EFV if:
  - >3yr+/>10kg

SA National DoH combined ARV guidelines 2015
How quickly do children respond to ART?

• Depending on regimen, co-treatment especially TB, adherence, absorption etc.

• Infants (median age 5.9 months)
  - 6 months: 28% suppression
  - 12 months: 56% suppression

• In study environments where VL are closely monitored VL suppressed as early as 12 weeks with INSTI’s (eg raltegravir and dolutegravir)

Porter, JAIDS, 2015; Nachman, CID, 2014
Children are more likely to develop VF +- resistance

- Poor adherence
  - Palatability of ART
  - Pill burden
  - Formulations eg no dispersible ABC/3TC & FDCs uncommonly available

- Treatment of co-disease especially TB
- Dependency on adult
- PMTCT exposure
- Socio-economic factors

Adolescents:
- psychological and structural barriers
- peer acceptance
- disclosure
- emotional challenges of puberty
Case study
BN
History: DoB 6 Feb 2014

- Presented to Hospital with moderate respiratory distress May 2014
- Known HEU until then, received 6 weeks NVP, Maternal VL unknown
- In wards diagnosed with
  - Pulmonary TB
  - PCP
- Discharged on standard doses TB Rx, kaletra, ABC, 3TC
• Seen in ward OPD and doses not adjusted
• No super-boosting LPV/r or double dosing with TB Rx
• Eventually booked at HIV clinic February 2015.....under-dosing for 6 months
• Doses corrected but too late......

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>CD4 #</td>
<td>2741</td>
<td>2113</td>
<td></td>
<td></td>
<td></td>
<td>2165</td>
</tr>
<tr>
<td>CD4%</td>
<td>40.7</td>
<td>35.67</td>
<td></td>
<td></td>
<td></td>
<td>45.1</td>
</tr>
<tr>
<td>VL</td>
<td>19651</td>
<td>11530</td>
<td>201588</td>
<td>41014</td>
<td>80</td>
<td>&lt;40</td>
</tr>
</tbody>
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DRT
Referred for a study
Child referred for P1093, a dolutegravir study in children, doing very well
How are we doing with the 3rd 90?

Viral Suppression (<400 copies/ml), 0-19 years at 12 months
July 2015-July 2017
Source: Tier.Net

<table>
<thead>
<tr>
<th>Month</th>
<th>VL done at 12 months</th>
<th>VL done Suppressed</th>
<th>VL Supression rate</th>
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<tbody>
<tr>
<td>Jul-Sep 15</td>
<td>47</td>
<td>65</td>
<td>72.3</td>
</tr>
<tr>
<td>Oct-Dec 15</td>
<td>41</td>
<td>61</td>
<td>67.2</td>
</tr>
<tr>
<td>Jan-Mar 16</td>
<td>50</td>
<td>67</td>
<td>89</td>
</tr>
<tr>
<td>Apr-Jun 16</td>
<td>59</td>
<td>73</td>
<td>75.3</td>
</tr>
<tr>
<td>Jul-Sept 16</td>
<td>56</td>
<td>82</td>
<td>68.5</td>
</tr>
<tr>
<td>Oct-Dec 16</td>
<td>61</td>
<td>72.0</td>
<td>84</td>
</tr>
<tr>
<td>Jan-Mar 17</td>
<td>44</td>
<td>83</td>
<td>66.7</td>
</tr>
<tr>
<td>Apr-Jun 17</td>
<td>20</td>
<td>78</td>
<td>73.5</td>
</tr>
<tr>
<td>Jul-17</td>
<td>14</td>
<td>56.4</td>
<td>70.0</td>
</tr>
</tbody>
</table>
FIG. 1. Estimated cascade of care in HIV-infected youth (ages 13–29 years) in the United States.
## Viral Load Monitoring and Recommended Responses

<table>
<thead>
<tr>
<th>Viral Load (VL)</th>
<th>Response</th>
</tr>
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<tbody>
<tr>
<td>&lt;50* copies/mL</td>
<td>12-monthly VL monitoring and routine adherence support</td>
</tr>
</tbody>
</table>
| 50*-1000 copies/mL | Repeat VL in 6 months  
Begin step-up adherence package if VL still between 50* – 1000 copies/mL |
| >1000 copies/mL | Begin step-up adherence package  
Repeat VL in 2 months  
If <50*, return to routine VL monitoring as above  
If between 50 and 1000 copies/mL, continue step-up adherence and repeat VL after 6 months  
If >1000 copies/mL, despite stepped up adherence support, AND child is on an NNRTI-based regimen, discuss with expert regarding new regimen.  
If >1000 copies/mL and child is on a PI-based regimen:  
Reinforce adherence (very difficult to fail a PI-based regimen unless the child received unboosted PI or was on rifampicin containing TB treatment while on a PI)  
Discuss with an expert regarding new regimen if VL >30,000 copies/mL,  
If the child received an unboosted PI (e.g. ritonavir alone) in the past or received TB treatment while on an LPV/r regimen and the VL is >1000 copies/mL, discuss with an expert regarding new regimen.  
Resistance testing is indicated in these situations but should only be done if the child has been reliably taking their ARVs in the past month. |
### Second-line ART regimens for children

#### Second-line regimen

**Failed first-line protease inhibitor (PI)-based regimen**

<table>
<thead>
<tr>
<th>Failed first-line PI-based regimen</th>
<th>Recommended second-line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC + 3TC + LPV/r</td>
<td></td>
</tr>
<tr>
<td>d4T + 3TC + LPV/r</td>
<td>Consult with expert for advice</td>
</tr>
</tbody>
</table>

**Unboosted PI-based regimen**

**Failed first-line NNRTI-based regimen (discuss with expert before changing)**

<table>
<thead>
<tr>
<th>Failed first-line NNRTI-based regimen (or NVP)</th>
<th>Recommended second-line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC + 3TC + EFV (or NVP)</td>
<td>AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td>d4T + 3TC + EFV (or NVP)</td>
<td>AZT + ABC + LPV/r</td>
</tr>
</tbody>
</table>

### 6.4.7 Third-line ART regimens

Children who fail second-line treatment should be referred to an expert so that the treatment with third-line agents can be considered.
Consequences of prolonged VL elevation and VF

Delayed switch is common
Management strategies after virologic failure during study follow-up

Weeks from Virologic Failure

- **Failing first-line**: 65 (7%)
- **Holding regimen**: 25 (3%)
- **Second-line**: 335 (34%)
- **Treatment Interruption**: 557 (57%)

Patten, *IWHOD*, 2017
What happens if we don’t switch?

• Many children are kept on a failing regimen
  - May need to improve adherence before switch
  - But sometimes in error
  - Do guidelines delay switch?

• Accumulation of resistance mutations particularly on an NNRTI-based regimen

• Risk of PI resistance mutations especially with previous TB co-treatment

= fewer future treatment options
Next steps

• Adherence counselling +++
• Don’t forget social determinants
• With NNRTI-based regimen switch as soon as possible
• Try to simplify regimen as much as possible eg once daily, lowest pill count, most palatable
• Need resistance testing if failing a PI
• May need to apply for a 3rd line regimen
Dolutegravir in Children
Integrase strand transfer inhibitors

• Dolutegravir has the following advantages:
  - Excellent resistance profile
  - Rapid VL suppression
  - Once daily (usually)
  - Reasonable side effect profile (but some concerns)

• Likely to be included in adult guidelines 2018

• FDA has approved 10 mg and 25 mg tablets for children > 6 years and > 30 kg

• P1093=IMPAACT study evaluating dosing and should be approved for younger ages in next few (months?) years
Conclusion

• Children and adolescents with VF and VL elevation need active management
• They have a lifetime of ART ahead of them= need as many drug options as possible
• Need to address adherence issues as successfully as possible-may be more difficult in children/adolescents
• Failure to do so has negative consequences (immediate and medium/long term)