1st Line Treatment Failure

&

2nd Line ART

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Outline

• Introduction - overview of treatment failure
• Revision of 1\textsuperscript{st} line ART regimens
• Monitoring treatment efficacy
• Recognition of treatment failure
• Causes of treatment failure
• Implications of treatment failure
• Switching regimens
• 2\textsuperscript{nd} line ART after NNRTI-based 1\textsuperscript{st} line regimen
• 2\textsuperscript{nd} line ART after PI-based 1\textsuperscript{st} line regimen
Introduction

• With expanding access to paediatric ART, children are more likely to experience treatment failure, subsequently requiring 2\textsuperscript{nd}-line therapy.\textsuperscript{1}
• Cumulative risk of failure increases over time.\textsuperscript{2}
• Paediatric data limited

Introduction

• IeDEA South Africa Cohort¹

  - looked at 5485 children across 7 different treatment sites (1999-2008)

  - 3 year probability of virologic failure
    = 19.3% (95% CI: 17.6 – 21.1)

Introduction

- **Cambodian Study (2007)**
  - 15% of children on 1\textsuperscript{st}-line ART had viral loads > 1000 copies/ml after 12 months of treatment

- **Chinese Study (2007)**
  - 37% of children on 1\textsuperscript{st}-line ART had viral loads > 1000 copies/ml after 12 months of treatment

- **Thai Study (2007)**
  - 17% of children on 1\textsuperscript{st}-line ART had viral loads > 1000 copies/ml after 12 months of treatment

# Western Cape 1st Line Antiretroviral Treatment Guidelines for Infants, Children and Early Adolescents

<table>
<thead>
<tr>
<th>All infants &gt;= 4 weeks old and children under 3 years (or&lt;10kg)</th>
<th>Abacavir + Lamivudine+ Lopinavir/Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children &gt;= 3 years (or &gt;= 10kg):</td>
<td></td>
</tr>
<tr>
<td>• NOT exposed to NVP during PMTCT</td>
<td>Abacavir + Lamivudine+ Efavirenz</td>
</tr>
<tr>
<td>• EXPOSED to NVP during PMTCT for 6 weeks or longer</td>
<td>Abacavir + Lamivudine+ Lopinavir/Ritonavir</td>
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# Monitoring Treatment Efficacy

<table>
<thead>
<tr>
<th>On ART</th>
<th>Purpose</th>
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</thead>
<tbody>
<tr>
<td>Height, weight, head circumference (&lt;2 years) and development</td>
<td>To monitor growth and developmental stages</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>To monitor response to ART and manage side effects</td>
</tr>
<tr>
<td>Hb and differential WCC at month 1, 2, 3 and 6 months (if on AZT)</td>
<td>To identify zidovudine-related anaemia</td>
</tr>
<tr>
<td>Cholesterol + Triglycerides at 1 year and then every 12 months if on PI-based regimen</td>
<td>To monitor for PI-related metabolic side-effects. Advise for dietary modification and refer for appropriate management if hyperlipidaemia present</td>
</tr>
<tr>
<td>Neurocognitive developmental assessments</td>
<td>With appropriate available tool</td>
</tr>
</tbody>
</table>
# Monitoring Treatment Efficacy

## On ART

<table>
<thead>
<tr>
<th>CD4: <strong>ALL</strong> at month 12</th>
<th><strong>Purpose</strong></th>
</tr>
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<tbody>
<tr>
<td>Then:</td>
<td>To monitor susceptibility to opportunistic infections and eligibility for Cotrimoxazole Preventive Therapy (CPT)</td>
</tr>
<tr>
<td>Children &lt; 5 years: every 12 months</td>
<td></td>
</tr>
<tr>
<td>Children &gt; 5 years: If CD4 &lt; 200 cells/mm³ repeat 6 monthly until &gt; 200 cells/mm³ - If CD4 &gt; 200 cells/mm³</td>
<td></td>
</tr>
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</table>

## VL: **ALL** at month 4 and 12

<table>
<thead>
<tr>
<th><strong>Purpose</strong></th>
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<tr>
<td>To monitor virological response to ART To identify treatment failure and problems with adherence</td>
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<tr>
<td>Then:</td>
</tr>
<tr>
<td>Children &lt; 5 years: every 6 months</td>
</tr>
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<td>Children &gt; 5 years: every 12 months</td>
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</table>
Recognition of Treatment Failure

- Clinical deterioration
  - poor growth / FTT
  - delay in developmental milestones
  - development of opportunistic infections

- Immunological deterioration
  - steady decline in CD4$^+$ count

- Unsuppressed HIV viral load
Recognition of Treatment Failure

• Viral Load (VL) 40 – 1000 copies/ml → Intensify adherence

• **NNRTI-based regimen** - VL > 1000 copies/ml (>=log 3) on 2 separate occasions, at least 8 – 12 weeks apart (after adherence has been addressed)

• **PI-based regimen** - VL > 1000 copies/ml (>=log 3) on 3 separate occasions, at least 8 – 12 weeks apart (after adherence has been addressed)
Causes of Treatment Failure

- **Intolerance of medication**
  - unpalatable formulations (eg: kaletra syrup)
  - side – effects (GIT, CNS)

- **Drug Toxicity**

- **Co-morbidities**
  - malabsorption
  - gastroenteritis

- **Caregiver problems**
  - physical health
  - mental health (denial, depression)
  - substance abuse
  - multiple caregivers

- **Failure to disclose to family and household members**

- **Financial / Access to care**
Implications of Treatment Failure

• Poor growth
• Developmental delay
• Associated co-morbidities
• Resistance – to specific drug
  – cross-resistance to drugs within same class
    limits options for subsequent drug regimens
Cross-Resistance

- Resistance to a drug which has never been used, that is acquired as a result of exposure to another drug, usually from the same class of ART drugs

- **NRTI**
  - d4T $\leftrightarrow$ AZT
  - 3TC $\leftrightarrow$ FTC
  - ABC $\leftrightarrow$ ddI

- **NNRTI**
  - NVP $\leftrightarrow$ EFV
  - NVP $\leftrightarrow$ ETR

- **PI**
  - uncommon when boosted
  - robust drug
  - unboosting / crushing of alluvia tablets leads to PI resistance
Reasons for Developing Resistance

• Archived NNRTI resistance (PMTCT – exposed)
• Delayed switching of regimens
  - failure to recognise virologic failure early
  - difficulty in assessing adherence
  - lack of access to drugs
  - fewer treatment options for children
  - limited access to resistance testing
Switching Regimens

- Low/middle income countries
  - programmatic approach
  - standardised 1\textsuperscript{st} and 2\textsuperscript{nd} line regimens
  - often lack of access to resistance testing
- In South Africa, policy has been revised and resistance testing has become more readily available, provided certain criteria have been met
Switching Regimens

• Address adherence issues before switching to another regimen

• Ensure caregivers have been adequately counselled
  – reasons for switching
  – new regimens

• Ensure correct regimen has been selected

• At least 2 new drugs should be used in new regimen

• Preferably 1 new drug class
Switching Regimens

Delay in switching leads to an increased risk of accumulating mutations, leading to an increased risk of developing drug resistance.
## Western Cape 2\textsuperscript{nd} Line Antiretroviral Treatment Guidelines

<table>
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<tr>
<th>2\textsuperscript{nd} Line Regimen (&lt; 15 years and &lt; 40kg)</th>
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<tbody>
<tr>
<td><strong>Failed 1\textsuperscript{st} line NNRTI based regimen</strong></td>
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<tr>
<th>First line NNRTI-based regimen:</th>
<th>Recommended second line regimen:</th>
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<tbody>
<tr>
<td>Abacavir + Lamivudine + Efavirenz (or Nevirapine)</td>
<td>Zidovudine + Lamivudine + Lopinavir/ritonavir</td>
</tr>
<tr>
<td>Stavudine + Lamivudine + Efavirenz (or Nevirapine)</td>
<td>Zidovudine + Lamivudine + Lopinavir/ritonavir</td>
</tr>
<tr>
<td>First line PI-based regimen:</td>
<td>Recommended second line regimen:</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Abacavir + Lamivudine + Lopinavir/ritonavir</td>
<td><em>Manage as for 3rd line regimens</em></td>
</tr>
<tr>
<td>Stavudine + Lamivudine + Lopinavir/ritonavir</td>
<td>Should be managed by a Paediatric Infectious Disease Specialist on the basis of genotype resistance testing.</td>
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**Indications for resistance testing:**
- Infants <2 years of age who are newly diagnosed as HIV positive if their mothers were exposed to PI-based ART during pregnancy or breastfeeding.
- Patients on a PI regimen with virological non-suppression defines as at least three viral load measurements of >= 1000 copies/ml (>=log 3) at least 8-12 weeks apart after adherence has been addressed.
Resistance Testing

• Can only be used to detect resistance to drugs currently being taken or within 4 weeks of stopping them
  - won’t necessarily show resistance to drugs patient was previously exposed to
• Is useful to exclude drugs from a future regimen
  - won’t necessarily indicate which drugs will work
• The viral load of the patient needs to be > 1000 copies/ml for reliable interpretation
• Ensure adherence is optimal
• Is not good at detecting minor variants (<20% of viral population)
• Very expensive
• Requires expert consultation for interpretation
Resistance Testing
Resistance Testing

Allows clinician to tailor regimen according to the patient’s age, drug history and availability of drugs
2nd Line Antiretroviral Treatment Options for a Failed 1st Line PI-Based Regimen

- No standardised regimen for children failing a 1st line PI-based regimen
- Largely depends on results of genotype resistance testing
- Currently using drugs previously reserved for 3rd line regimens
Darunavir (DRV)

• Protease Inhibitor

• Requires boosting with Ritonavir (RTV)

• Do not use in children < 3 years or < 10kg
  - concerns related to seizures and death in infant rats

• Twice daily dosing with food
Raltegravir (RAL)

- Integrase inhibitor

- Do not use in children < 4 weeks of age or < 3kg – metabolism a problem

- Twice daily dosing with or without food
Etravirine (ETR)

- NNRTI

- Do not use in children < 6 years of age or < 16kg

- Studies in children aged 2 months – 6 years are currently underway

- Twice daily dosing with food
Atazanavir (ATV)

- Protease Inhibitor

- Requires boosting with Ritonavir

- Do not use in infants and neonates < 3 months of age
  - concerns of hyperbilirubinemia in neonates

- Twice daily dosing with food
Summary

• AAA

• Anticipate and identify treatment failure early

• If in doubt, consult an expert

• ‘Don’t delay, switch today’