HAART in children
Overview

• When do we start?
• What are the classes of drugs?
• What drugs do we use?
• How to start
• Side-effects
• Adherence
• Co-treatment for TB
• IRIS
OBJECTIVES

• List the SA guidelines on starting HAART in children
• Define all the criteria to be filled before initiating HAART in a child
• Describe the regimens used in children
• Identify children eligible for HAART
• Discuss management and follow up of children who don’t qualify for HAART
• Monitor a child on HAART
OBJECTIVES

• Understand immune reconstitution in children
• Explain initiation of HAART in children receiving TB treatment
• Explain interactions of TB therapy and HAART
• Identify side effects in children and discuss the management thereof
• Discuss situations in which changing or stopping HAART would be appropriate
• 5.23 million South Africans infected by the end of 2007

• Women bear the burden of the HIV epidemic

• Among the 10% of infected youth, 61% are female

• About 280 000 children are living with HIV
Viral dynamics in children

- Viral loads are higher \textbf{in the first year of life}
- Decline to adult values by 5 - 6 years of age
Viral load in adults

Plasma HIV RNA levels in Adults

Viral load no. copies/mL (log)

Months/Years
Viral load in children

Plasma HIV RNA levels in Infants

Viral load no. of copies/mL (log)

1 10 100 1000 10000 100000 1000000

1 2 2.5 3
years
Months/Years
Natural progression continued…

• HIV infects and destroys the T helper cells
• Rate of viral replication directly related to the rate at which immune system is destroyed
• Response to HIV varies widely between individuals, ranges: **Rapid Intermediate** and **Slow/ long term-progressors**
• In the absence of ART median time to AIDS is 8 - 10 years (developing/developed world)
## Patterns Of HIV Disease In Children

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non Progressor</strong></td>
<td>Often shows no obvious signs of HIV infection.</td>
</tr>
<tr>
<td></td>
<td>Can be well for a very long time.</td>
</tr>
<tr>
<td></td>
<td>May survive for a long time with low viral load and good CD4 count even without ART.</td>
</tr>
<tr>
<td></td>
<td>Able to keep the viral load with which they were infected low.</td>
</tr>
<tr>
<td></td>
<td>5 – 10% of children</td>
</tr>
<tr>
<td><strong>Slow Progressor</strong></td>
<td>May start getting ill from HIV in the toddler years.</td>
</tr>
<tr>
<td></td>
<td>Gets sicker slower</td>
</tr>
<tr>
<td></td>
<td>May survive even without ART into the early teens.</td>
</tr>
<tr>
<td></td>
<td>May be infected with a lower viral load (eg through breastfeeding)</td>
</tr>
<tr>
<td></td>
<td>50 - 60% of children</td>
</tr>
<tr>
<td><strong>Rapid Progressor</strong></td>
<td>Usually will show signs of HIV infection before 1 year of age.</td>
</tr>
<tr>
<td></td>
<td>Gets very sick very quickly</td>
</tr>
<tr>
<td></td>
<td>If untreated may die by the age of 2 years</td>
</tr>
<tr>
<td></td>
<td>Often infected with a high viral load (sick mother or newly infected mother)</td>
</tr>
<tr>
<td></td>
<td>25 - 30 % of children</td>
</tr>
</tbody>
</table>
Patterns Of HIV Disease In Children

3 different patterns of HIV disease in babies & children:

- NON Progressor
- SLOW Progressor
- RAPID Progressor
Patterns Of HIV Disease In Children

3 different patterns of HIV disease in babies & children:

- NON Progressor
- SLOW Progressor
- RAPID Progressor
Patterns Of HIV Disease In Children

- **NON Progressor**
  - Green bus

- **SLOW Progressor**
  - Blue bus

- **RAPID Progressor**
  - Red bus

Additional Notes:
- STOP sign
- ARV bottle
- Heart pattern border
When To Start?

- CHER Study
When To Start: SA Guidelines

Recurrent hospitalisations
- > 2 admissions per year

Prolonged hospitalisation
- > 4 weeks) for HIV complications
  - New guidelines……??
Draft SA Guidelines Revision

- **<12 months**
  - All HIV infected children
  - Regardless of WHO staging and CD4 count

- **12 months – 5 years**
  - WHO III, IV
  - CD4% < 20%

- **>5 years**
  - Stage III or IV
  - CD4 count < 200 or < 15%
Psychosocial Criteria

Children D.O.H Guidelines

**Mandatory**
At least one identifiable caregiver who is able to supervise child or administer medication

**Recommended**
Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child’s ART

*(Do not exclude orphans and the abandoned)*
Preparing A Child For ART

- Establish a definitive HIV diagnosis and WHO stage the patient
- Screening CD4%
- Exclude TB (treat if suspicious)
- Treat intercurrent illnesses and OIs first
- Identify responsible person to administer treatment.
- Optimise caregiver and family health
- Counsel, educate and demonstrate about ART
<table>
<thead>
<tr>
<th>CLASS</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reverse Transcriptase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Nucleoside - Thymidine Analogues</td>
<td>Zidovudine (AZT)</td>
</tr>
<tr>
<td></td>
<td>Stavudine (d4T)</td>
</tr>
<tr>
<td>Nucleoside – Non-Thymidine Analogues</td>
<td>Didanosine (ddI)</td>
</tr>
<tr>
<td></td>
<td>Lamivudine (3TC)</td>
</tr>
<tr>
<td></td>
<td>Abacavir (ABC)</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine (FTC)</td>
</tr>
<tr>
<td>Nucleotide</td>
<td>Tenofovir (TDF)</td>
</tr>
<tr>
<td>Non-Nucleoside</td>
<td>Nevirapine (NVP)</td>
</tr>
<tr>
<td></td>
<td>Efavirenz (EFZ)</td>
</tr>
<tr>
<td><strong>Protease Inhibitors (PI)</strong></td>
<td>Lopinavir / Ritonavir Kaletra</td>
</tr>
<tr>
<td></td>
<td>Ritonvir</td>
</tr>
<tr>
<td></td>
<td>Saquinavir</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir</td>
</tr>
<tr>
<td></td>
<td>Atazanavir</td>
</tr>
<tr>
<td></td>
<td>Indinavir</td>
</tr>
<tr>
<td><strong>Fusion Inhibitors</strong></td>
<td>Enfuviritide</td>
</tr>
</tbody>
</table>
Classes Of Drugs

NRTI’s
- Nucleoside reverse transcriptase inhibitors
- Thymidine Analogue
- Non-thymidine Analogue

NNRTI’s
- Non-nucleoside reverse transcriptase inhibitors

PI’s
- Protease inhibitors
Thymidine Analogue

d4T- stavudine, Zerit®

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Major Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dose 1mg/kg</td>
<td>• Well tolerated in the short term</td>
</tr>
<tr>
<td>• No relation to food</td>
<td>• Pancreatitis, peripheral neuropathy, lipoatrophy, lactic acidosis.</td>
</tr>
<tr>
<td>• Keep syrup in fridge</td>
<td>• Occurs after 4 months</td>
</tr>
</tbody>
</table>
# Thymidine Analogue

**AZT - zidovudine, Retrovir®**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose is 180mg/m²</td>
<td>Short term: nausea, headache and malaise</td>
</tr>
<tr>
<td>No relationship to food</td>
<td>Long term: marrow suppression, myopathy, fingernail discoloration.</td>
</tr>
</tbody>
</table>
### Non Thymidine Analogue

#### 3TC- Lamivudine, Epivir®

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No relationship to food.</td>
<td>• Very few- relationship to pancreatitis in hemophiliac children.</td>
</tr>
<tr>
<td></td>
<td>• Peripheral neuropathy</td>
</tr>
</tbody>
</table>

---

**No relationship to food.**

- Very few- relationship to pancreatitis in hemophiliac children.
- Peripheral neuropathy
Non thymidine analogue

**ddl- didanosine, Videx® (buffered, EC)**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Side effects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose is 180-240mg/m²</td>
<td>Pancreatitis, peripheral neuropathy, lactic acidosis</td>
</tr>
<tr>
<td>Relationship to food – ½ hour before food or 2 hours after, always give 2 tablets, separate from Kaletra by two hours</td>
<td></td>
</tr>
</tbody>
</table>
## Non Thymididine Analogue

### ABC- Abacavir, Ziagen ®

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less hepatotoxicity than others</td>
<td>• Guanidine analogue</td>
</tr>
<tr>
<td>Potentially life-threatening hypersensitivity</td>
<td>Dose 8 mg/kg bd</td>
</tr>
<tr>
<td>Do not rechallenge if hypersensitivity reaction</td>
<td>• Keep syrup in fridge</td>
</tr>
<tr>
<td>• Less mitochondrial toxicity than other NRTI’s</td>
<td></td>
</tr>
</tbody>
</table>
# Boosted PI

## Lopinavir/Ritonavir - Kaletra®

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose is 230-300mg/m²</td>
<td>Short term side effect GIT</td>
</tr>
<tr>
<td>Stored in the fridge</td>
<td>CLASS EFFECT insulin resistance, fat accumulation and hypertrygleriadaemia</td>
</tr>
</tbody>
</table>
### NNRTI

**Efavirenz- Stocrin®**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>See next slide</td>
<td>Neuropsychiatric, rash.</td>
</tr>
<tr>
<td></td>
<td>Teratogenic</td>
</tr>
</tbody>
</table>

**Nevirapine- Viramune®**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase dose after 2 weeks if tolerated</td>
<td>Hepatotoxic, rash.</td>
</tr>
</tbody>
</table>
Efavirenz dose

- Start: 10kg and 200mg
- Go up with: 5kg and 50mg
- Exception: 33kg not 30kg
Which Drugs Do We Use?

- Nothing less than 3 drugs
- Usually 2 NRTI’s + either NNRTI or PI
- Few new drugs being tested
## Regimens For Children

(DOH Guidelines)

<table>
<thead>
<tr>
<th></th>
<th>Less than 3 years</th>
<th>&gt;3 years (&gt;10kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line</strong></td>
<td>stavudine (d4T) lamivudine (3TC) kaletra®</td>
<td>stavudine (d4T) lamivudine (3TC) efavirenz (Stocrin)</td>
</tr>
<tr>
<td><strong>2nd line</strong></td>
<td>zidovudine (AZT) didanosine (ddI) efavirenz/NVP</td>
<td>zidovudine (AZT) didanosine(ddI) kaletra®</td>
</tr>
</tbody>
</table>
## Nevirapine Resistance

### NVP Resistance Detected Post Single Dose NVP for PMTCT

- ~25-40% women
- ~40-90% babies

### Implications for Future NVP-Based Treatment Regimen

- Women > 6 months post delivery → viral suppression (Mashi Plus)
- < 6 months post delivery ↑ risk of virological failure NVP arm (Lockman et al Mashi Plus Study, Botswana 2005)
- Neverest 1

### Data Required for Infants

- Mashi Plus study - 15 children each in non-NVP vs NVP treatment arms → significant ↑ risk virological failure in NVP arm
- Neverest (Coronation Hospital, Johannesburg)
- PACTG 1060 (Ongoing multicentre African sites)
ARV Dosing

- Doses must be adjusted for weight as children grow
- Standardised weight tables (WHO) in DOH guidelines
- Some formulations also use Body Surface Area (BSA) especially for children under 1 year (Lop/r, ddI, NVP, Ritonavir)

\[ \text{BSA (m}^2\) = \sqrt{\frac{\text{height (cm) x weight (kg)}}{3600}} \]
### Antiretroviral Drug Dosing Chart for Children (2007)

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Stavudine (d4T)</th>
<th>Lamivudine (3TC)</th>
<th>Zidovudine (AZT)</th>
<th>Didanosine (ddI)</th>
<th>Abacavir (ABC)</th>
<th>Efavirenz (EFV)</th>
<th>Nevirapine (NVP)</th>
<th>Lopinavir/Ritonavir (LPV/ritv)</th>
<th>Ritonavir boosting (RTV)</th>
<th>Cotrimoxazole</th>
<th>Multivitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>Consult with a clinician experienced in pediatric ARV prescribing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-6.9</td>
<td>8ml</td>
<td>3ml</td>
<td>8ml</td>
<td>2x0.5mg tabs</td>
<td>2ml</td>
<td>Dosing &lt;10kg not established</td>
<td>6ml</td>
<td>6ml</td>
<td>1ml</td>
<td>2.5ml</td>
<td>2.5ml</td>
</tr>
<tr>
<td>6.9-7.9</td>
<td>7ml</td>
<td>6ml</td>
<td>8ml</td>
<td>2ml</td>
<td>4ml</td>
<td>2ml</td>
<td>2ml</td>
<td>2ml</td>
<td>1.5ml</td>
<td>3ml or 1/2 tab</td>
<td><strong>1.5ml</strong></td>
</tr>
<tr>
<td>7.9-8.9</td>
<td>6ml</td>
<td>5ml</td>
<td>8ml</td>
<td>3x0.5mg tabs am, pm</td>
<td>3x0.5mg tabs pm</td>
<td>6ml</td>
<td>200mg cap</td>
<td>10ml or 1/2 tab</td>
<td>10ml or 1/2 tab</td>
<td>3ml or 1/2 tab</td>
<td><strong>1.5ml</strong></td>
</tr>
<tr>
<td>8.9-9.9</td>
<td>5ml</td>
<td>4ml</td>
<td>8ml</td>
<td>2x0mg tabs am, pm</td>
<td>2x0mg tabs pm</td>
<td>6ml</td>
<td>200mg cap + 50mg cap</td>
<td>1 tab, 1/2 tab pm</td>
<td>1 tab, 1/2 tab pm</td>
<td>2.5ml bd or 2 caps pm</td>
<td><strong>2.5ml</strong></td>
</tr>
<tr>
<td>9.9-11.9</td>
<td>4ml</td>
<td>3ml</td>
<td>8ml</td>
<td>2x0mg tabs am, pm</td>
<td>2x0mg tabs pm</td>
<td>6ml</td>
<td>200mg cap + 2x50mg caps</td>
<td>3ml or 2 caps</td>
<td>3.5ml or 2 caps</td>
<td><strong>3.5ml</strong></td>
<td></td>
</tr>
<tr>
<td>11.9-13.9</td>
<td>3ml</td>
<td>2ml</td>
<td>7ml</td>
<td>1 x 0mg tabs am, pm</td>
<td>1 x 0mg tabs pm</td>
<td>6ml</td>
<td>200mg cap + 3x50mg caps</td>
<td>4ml or 3 caps</td>
<td>5ml or 3 caps</td>
<td><strong>5ml</strong></td>
<td></td>
</tr>
<tr>
<td>13.9-15.9</td>
<td>2ml</td>
<td>1ml</td>
<td>6ml</td>
<td>1 tab</td>
<td>1 tab</td>
<td>600mg tab</td>
<td>20mg or 2 tabs</td>
<td>1 tab</td>
<td>1 tab</td>
<td><strong>8 ml</strong></td>
<td></td>
</tr>
<tr>
<td>15.9-30.9</td>
<td>1ml</td>
<td>600mg tab</td>
<td>20mg or 2 tabs</td>
<td>1 tab</td>
<td>1 tab</td>
<td>600mg tab</td>
<td>20mg or 2 tabs</td>
<td>1 tab</td>
<td>1 tab</td>
<td><strong>8 ml</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Induction refers to a lead-in dose of nevirapine for the first 14 days of treatment equivalent to half of maintenance dose i.e. usual maintenance dose but given once-daily. Increase to full maintenance dose after 14 days if no rash develops.

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Body Surface Area (BSA) m² = \[
\frac{\text{Weight (kg)} \times \text{Height (cm)}}{1800}
\]
Pharmaceutical Challenges for Paediatric ART

- Fewer formulations available for children than for adults
- Liquids often unpalatable or only available in large volumes
- Long-term toxicities in children? Eg effects on bone development TDF
- Adult formulations used for children
Fixed Dose Combinations (FDC)

• Urgent need for formulations that will maximise adherence and minimise toxicity
• WHO drafting recommendations for FDC’s for children with an expert international panel
• Urging pharmaceutical industry to develop solid FDC’s (child friendly; crushable, chewable, dispersible, scored tablets)
• Aim for harmonized dosing strategy for FDC’s
  – both existing and “yet to be developed” formulations should become part of a dose by weight band system
Monitoring

(DoH Guidelines)

- Baseline CD4, Viral Load, FBC, ALT, Chol, Triglycerides
- 2 week adherence & tolerance visit
- 1-month visit, and 3-monthly clinical exam
- 6-monthly CD4, Viral load unless indicated otherwise
- Annual chol and triglycerides
- Toxicity depending on drug regimen
Viral Load

- One log drop by 4 weeks
- Undetectable by 24 weeks (<50)
- Thereafter every 6 months
- Viral blips
- If above 1000 copies/ml confirm with a second test. Increase adherence counseling.
Side Effects (Adverse Events)

• In general, side effects are less common in children

• Same spectrum of side effects that occur in adults reported in children.
  – Some are rare in children, e.g. NVP-related symptomatic hepatotoxicity
  – Some are more common, e.g. NVP and EFV-related rash
  – Some occur only in children, e.g. Tenofovir-related loss of bone density
Complications of HIV and toxicity to other drugs can look like ARV-related side effects.

Always consider these too.

- HIV Hepatitis
- hepatitis A, B, C, other viruses eg. CMV, EBV
- INH
- Anaemia
- malaria
- Viral Exanthem
- Cotrimoxazole
11 days after starting HAART containing nevirapine, this 11 year old boy presented with Stevens-Johnson syndrome. Liver toxicity is often also present, though not in this case. For more details, see http://www.med.cmu.ac.th/dept/pediatrics/06-interest-cases/ic-74/page1.htm
Assistance for Children who don’t Qualify for HAART

- Monitor closely
- 3 monthly clinical exams (weight check, look out for OI’s etc.)
- WHO clinical staging at each visit
- 6 monthly CD4 measurements & other baseline bloods
Factors Affecting Adherence

- Lack of Transport
- Lack of Education
- Gender
- Finances
- Stigma
- Attitude of Health Providers
- Health Literacy
- Ill Health
- Feeling Better
- Food Insecurity
- Shame

ADHERENCE
Adherence Challenges

**Patient factors**
- Children are dependent on **care giver** (age, illness, poverty, relationship, etc.)
- Child may have developmental delay
- Family dynamics
- Disclosure
- Adolescence

**Medication factors**
- Formulations (EFV)
- Palatability (Kaletra, ritonavir)
- Storage (d4T)
- Dosing (Kaletra, EFV)
- Administration (d4T)
- High “pill” burden

**Provider/Site factors**
- Cost of treatment (outpatient fees, transport, work absenteeism, child care)
- Type of facility/resources
- HW communication skills
- Family care
Concomitant TB Rx and ART

- Treatment of TB takes priority
  - If TB treatment started first:
    - If possible complete TB treatment prior to starting ART, but if child is ill and:
      - Increasingly starting TB treatment early (2 weeks - 2 months)
      - If child has low CD4 count (<15%) and is clinically ill start after 2 weeks if ALT normal.
  - If ART started first:
    May require change in ART regimen, especially if on nevirapine or Kaletra.
Drug Interactions

Enzyme System Inhibitors / Inducers

**Enzyme System Inhibitors**
- ritonavir
- saquinavir
- indinavir
- nelfinavir
- grapefruit juice
- ketoconazole

**Enzyme System Inducers**
- rifampicin
- efavirenz
- nevirapine
- phenytoin
- St John’s wort
- garlic

**Metabolism**

**LIVER**

**Pis**

**NNRTIs**

**Enzyme system CYP450**
TB Rx and Kaletra

- Need to “boost” Kaletra (4:1 concentration lopinavir: Ritonavir)

Possibilities:

- Add Ritonavir to “boost” dose (1:1) – Best!!
- Double dose kaletra (use 600 mg/m²)
When To Change Treatment

- **Toxicity**
  - Short-term side-effects
  - Long-term side-effects
- **Treatment failure**
  - Clinical
  - Virological (Resistance)
  - Immunological
- **Drug interactions**
When To Change Treatment

- If serious adverse events
- **Clinical deterioration** (new stage III event) not TB or immune reconstitution – treatment
- Confirmed **declining CD4** or **increasing VL** not TB or other intercurrent infection
- **Viral load returned to baseline** (may tolerate – treatment - elevated VL if CD4 and clinical state still good)
  - Evaluate and optimise adherence if regimen failing!!!
  - Check dosing, rule out an occult OI
  - If uncertain consult an expert
Immune Reconstitution Disease

'Immune Reconstitution Syndrome'
'Immune Reconstitution Inflammatory Syndrome'

- Paradoxical clinical deterioration after starting HAART
- Less common in children than adults
- Usually affects those with very low starting CD4 % unless they have an underlying OI, CD4 may be higher
- Occurs within the first 3 months after the start of ART, concurrent with a rapid rise in CD4
- Clinical presentations depend on the causative organism and the organ-system that is colonised.
The Usual Suspects......

TB
MAC
Cryptococcal Meningitis
Herpes Zoster
Hepatitis B & C
CMV
PCP
PML
BCG IRIS
Dermatological IRIS
CHAIN OF SURVIVAL

EARLY ACCESS
EARLY CPR
EARLY DEFIBRILLATION
EARLY ADVANCED CARE
CHAIN OF SURVIVAL

EARLY ACCESS
EARLY CPR
EARLY DEFIBRILLATION
EARLY ADVANCED CARE
Case Study

A 5 year old girl has been referred to your clinic from private:

- ddI/d4T/EFZ for 6 months
- Her baseline CD4 count was 50 (3%) and VL 23 000 RNA copies/ml
- Her last VL was <400 RNA copies/ml and her CD4 percentage = 16% (455).
Case Study

She gives a week’s history of:

- Severe abdominal pain
- Seen at the Paediatric OPD for vomiting and treated for a mild GE.
- Now clinically mildly dehydrated and does not want any food due to the nausea and abdominal pain.
Case study

1. What do you think of her regimen?
2. What about her response to treatment?
3. What do you think is going on and how do you go about confirming your suspicions?
4. How could this have been predicted or avoided?
5. What regimen change if any would you make?
Before and After ART

6 Months Later
Before and After ART