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

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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

HIV in South Africa

- 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

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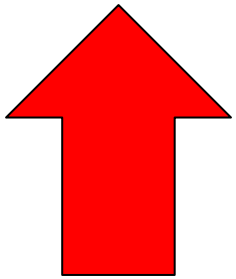
Viral dynamics in children

- Viral loads are higher **in the first year of life**
- Decline to adult values by 5 - 6 years of age



High viral load

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Faster disease progression

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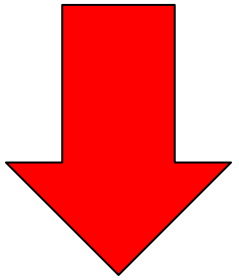
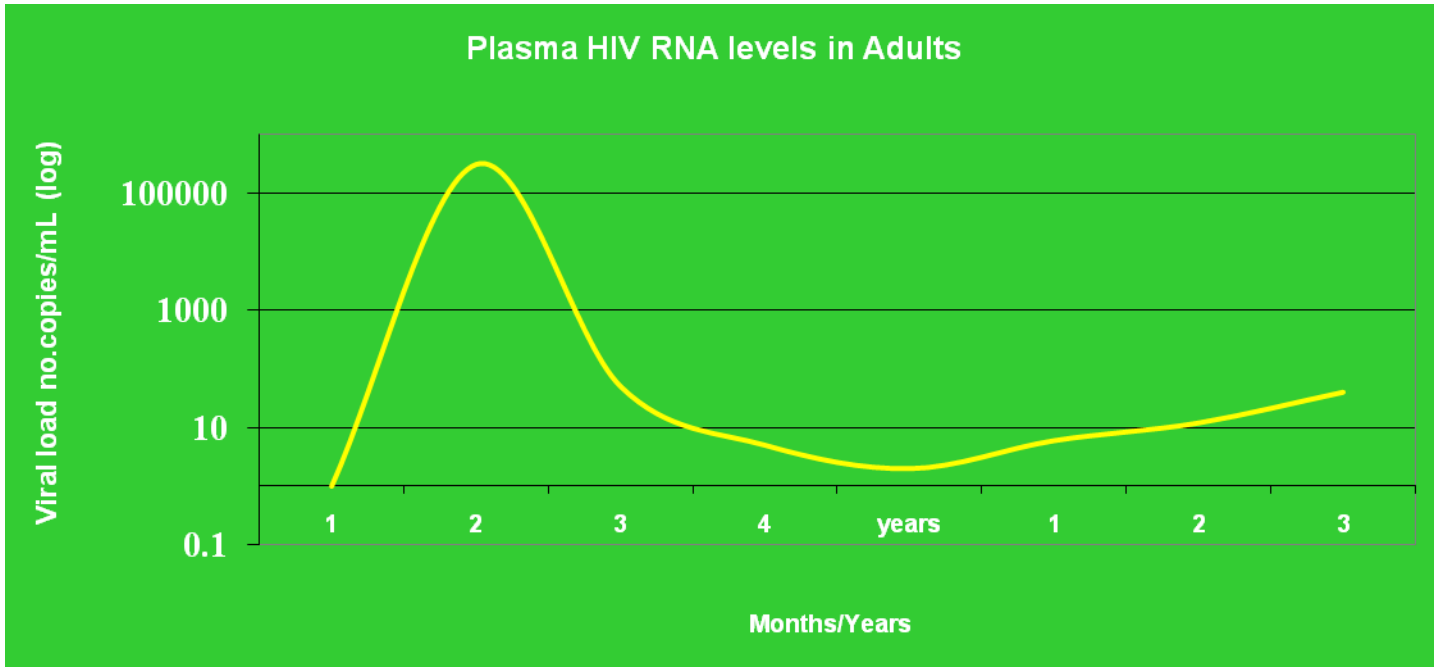


Shorter lifespan

Viral load in adults



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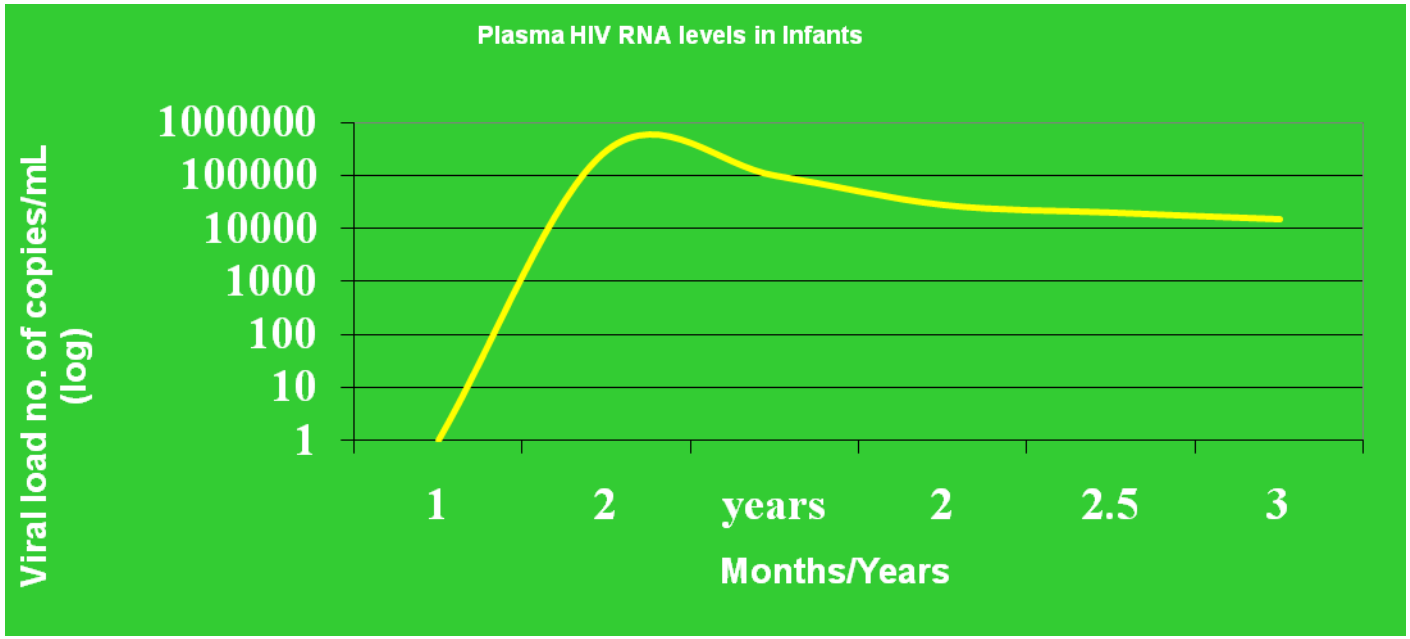
Viral load in children



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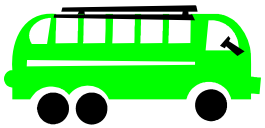
Natural progression continued…

- 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 widelv 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

NON Progressor



Often shows no obvious signs of HIV infection

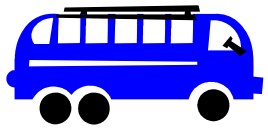
Can be well for a very long time

May survive for a long time with low viral load and good CD4 count even without ART

Able to keep the viral load with which they were infected low

5 – 10% of children

SLOW Progressor



May start getting ill from HIV in the toddler years

Gets sicker slower

May survive even without ART into the early teens.

May be infected with a lower viral load (eg through breastfeeding)

50 - 60% of children

RAPID Progressor

Usually will show signs of HIV infection before 1 year of age.

Gets very sick very quickly

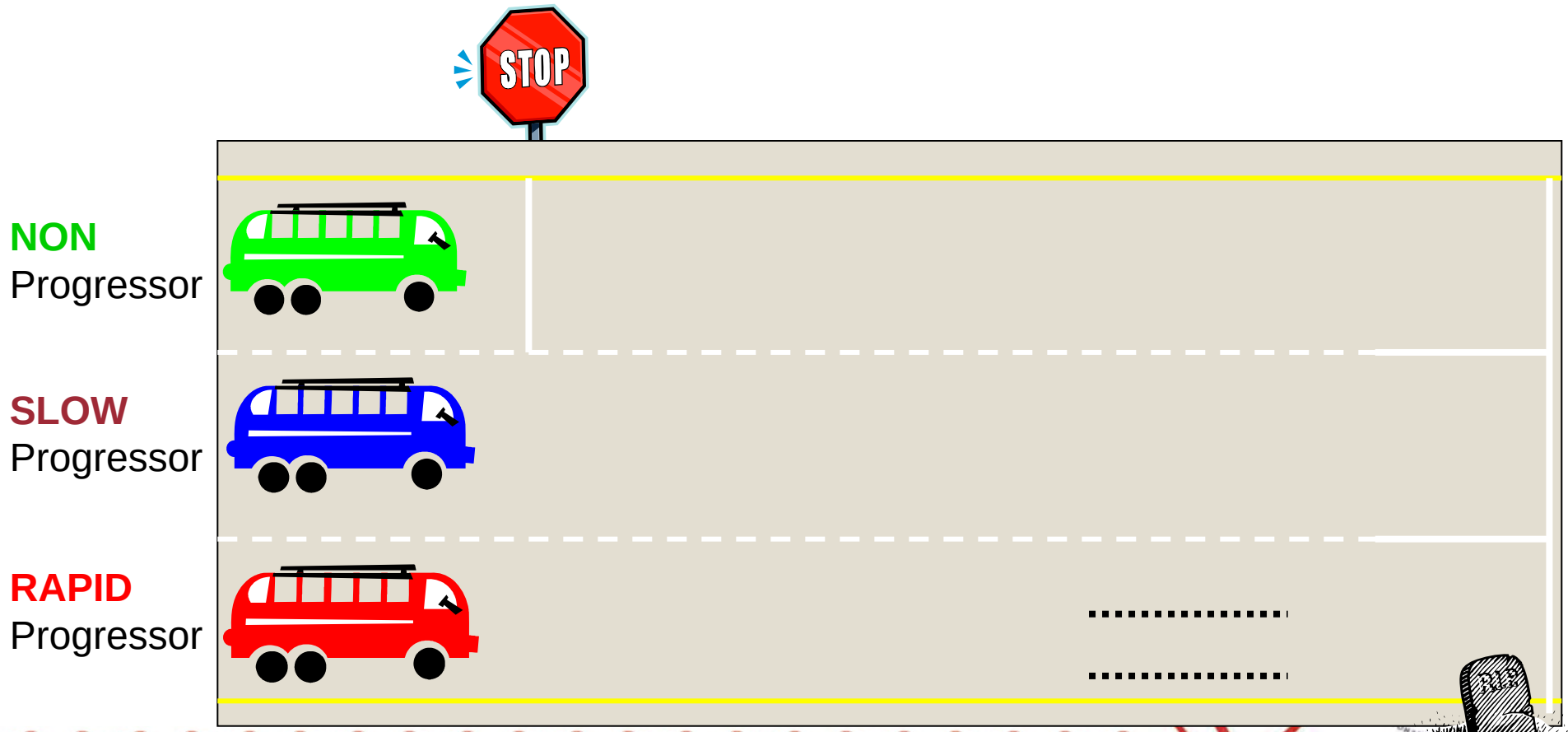
If untreated may die by the age of 2 years

Often infected with a high viral load (sick mother or newly infected mother)

25 - 30 % of children

Patterns Of HIV Disease In Children

3 different patterns of HIV disease in babies & children:



Patterns Of HIV Disease In Children

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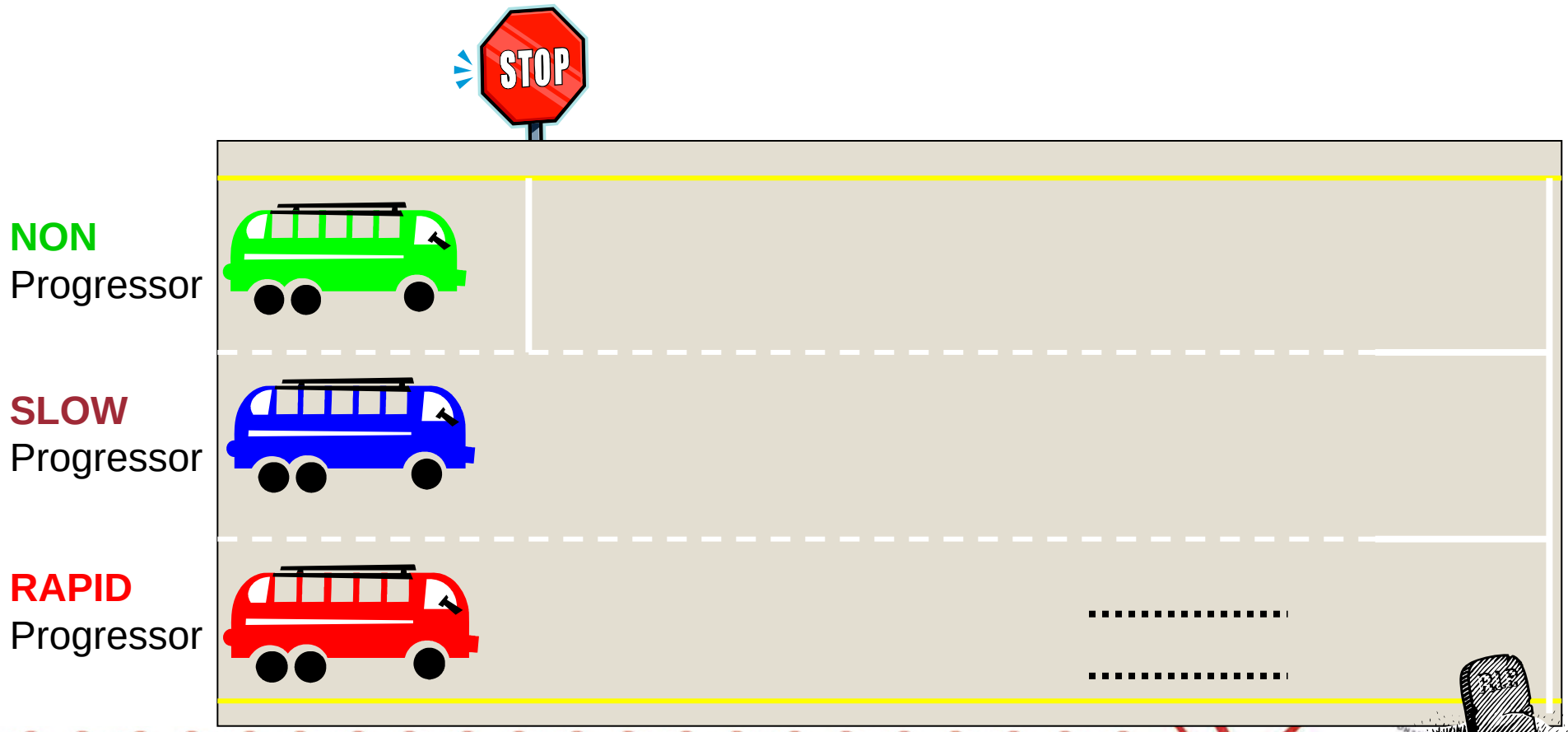
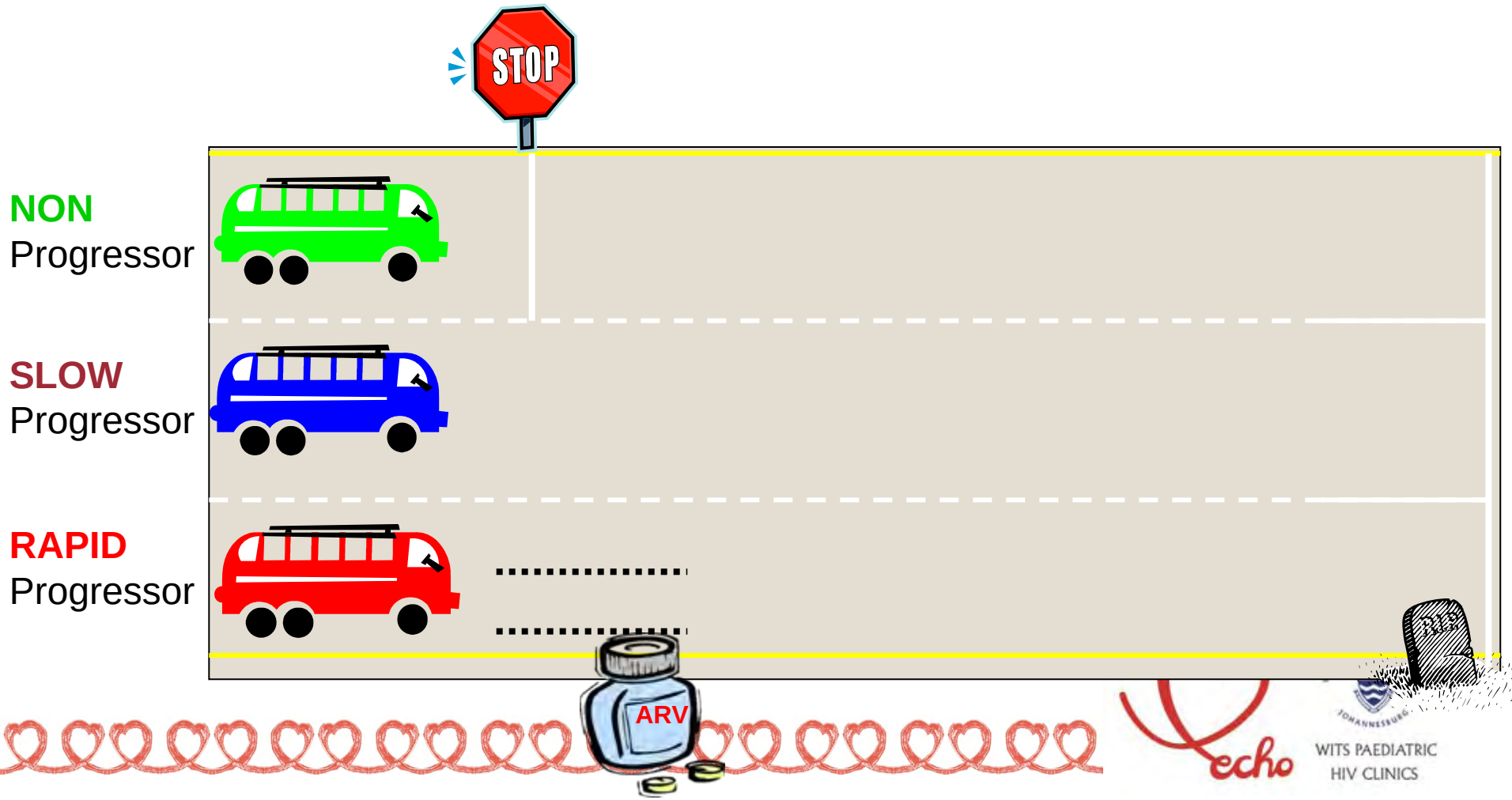
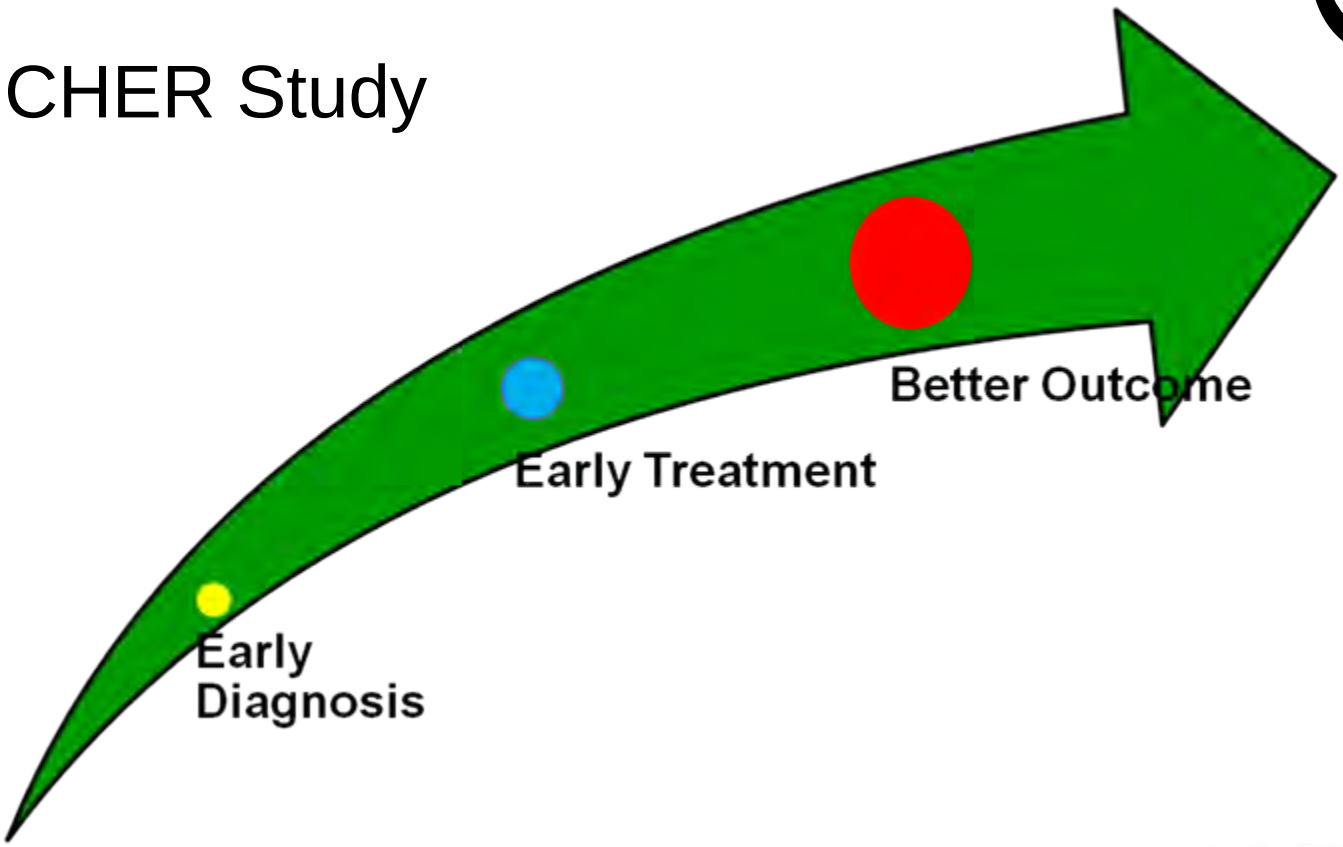


Patterns Of HIV Disease In Children



When To Start?

- CHER Study



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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	12 months – 5 years	>5 years
All HIV infected children	WHO III,IV	Stage III or IV
Regardless of WHO staging and CD4 count	CD4% <20%	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)

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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

CLASS		DRUG
Reverse Transcriptase Inhibitors	Nucleoside - Thymidine Analogues	Zidovudine (AZT)
		Stavudine (d4T)
	Nucleoside – Non-Thymidine Analogues	Didanosine (ddI)
		Lamivudine (3TC)
		Abacavir (ABC)
		Emtricitabine (FTC)
	Nucleotide	Tenofovir (TDF)
	Non-Nucleoside	Nevirapine (NVP)
		Efavirenz (EFZ)
Protease Inhibitors (PI)		Lopinavir / Ritonavir Kaletra
		Ritonvir
		Saquinavir
		Nelfinavir
		Atazanavir
		Indinavir
Fusion Inhibitors		Enfuviritide

Classes Of Drugs

NRTI's

- Nucleoside reverse transcriptase inhibitors
- Thymidine Analogues
- Non-thymidine Analogues

NNRTI's

- Non-nucleoside reverse transcriptase inhibitors

PI's

- Protease inhibitors

Thymidine Analogue

d4T- stavudine, Zerit®

Dosing
• Dose 1mg/kg
• No relation to food
• Keep syrup in fridge

Major Side Effects
• Well tolerated in the short term
• Pancreatitis, peripheral neuropathy, lipoatrophy, lactic acidosis.
• Occurs after 4 months

Thymidine Analogue

AZT- zidovudine, Retrovir®

Dosing
Dose is 180mg/m^2
No relationship to food

Side Effects
Short term: nausea, headache and malaise
Long term: marrow suppression, myopathy, fingernail discoloration.

Non Thymidine Analogue

3TC- lamivudine, Epivir®

Dosing
• No relationship to food.

Side effects
• Very few- relationship to pancreatitis in hemophiliac children.
• Peripheral neuropathy

Non thymidine analogue

ddI- didanosine, Videx® (buffered, EC)

Dosing
Dose is 180-240mg/m^2
Relationship to food – ½ hour before food or 2 hours after, always give 2 tablets, separate from Kaletra by two hours

Side effects.
Pancreatitis, peripheral neuropathy, lactic acidosis

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Non Thymidine Analogue

ABC- Abacavir, Ziagen ®

Side Effects
Less hepatotoxicity than others
Potentially life-threatening hypersensitivity
Do not rechallenge if hypersensitivity reaction
• Less mitochondrial toxicity than other NRTI's

Dosing
• Guanidine analogue
Dose 8 mg/kg bd
• Keep syrup in fridge

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Boosted PI

Lopinavir/Ritonavir- Kaletra®

Dosing
Dose is 230-300mg/m^2
Stored in the fridge

Side effects
Short term side effect GIT
CLASS EFFECT insulin resistance, fat accumulation and hypertrygleridaemia

NNRTI

Efavirenz- Stocrin®

Dosing	Side Effects
See next slide	Neuropsychiatric, rash. Teratogenic

Nevirapine- Viramune®

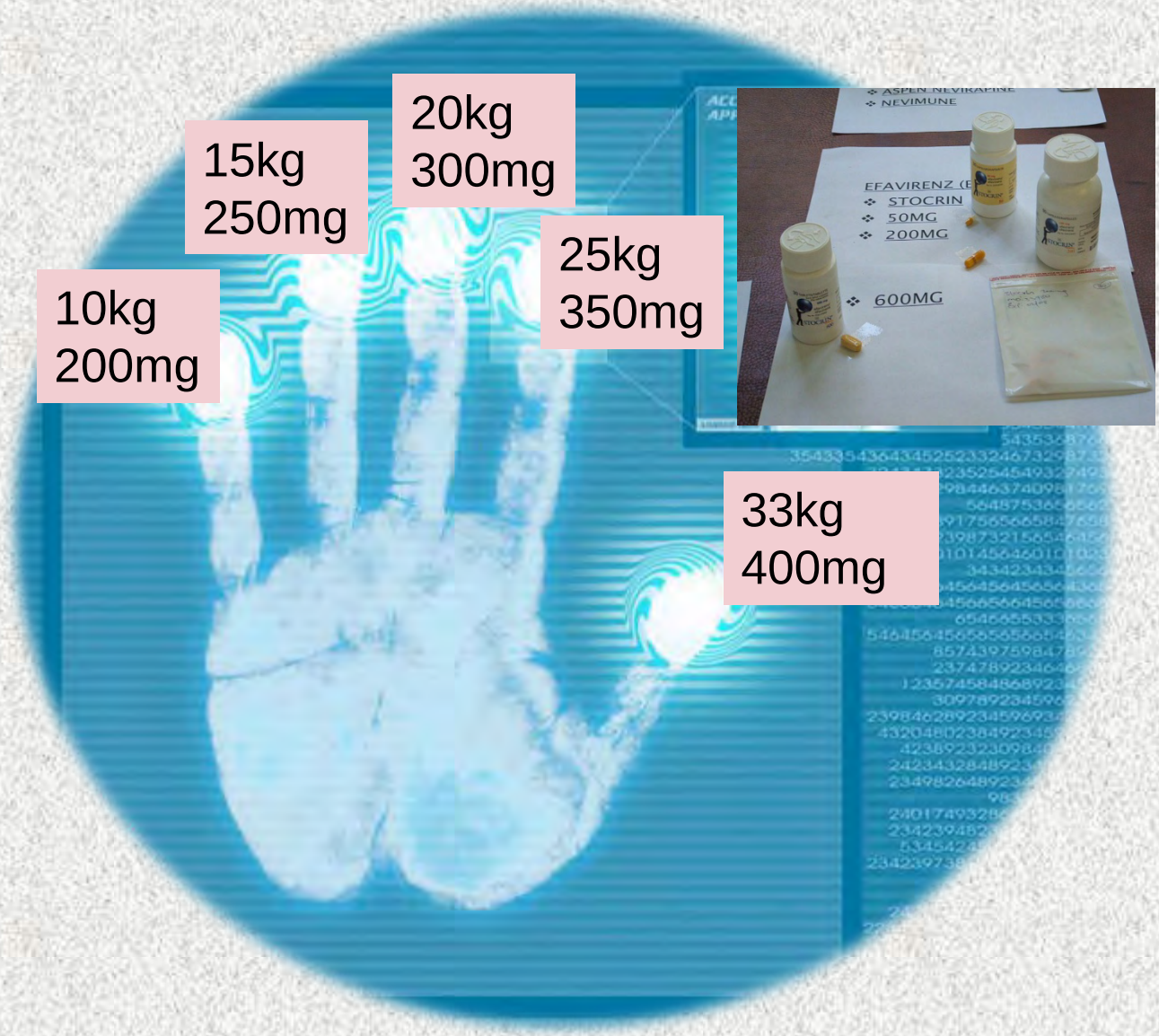
Dosing	Side Effects
Increase dose after 2 weeks if tolerated	Hepatotoxic, rash.

Efavirenz dose

-Start :
10kg
and 200mg

-Go up with:
5kg
and 50mg

- Exception:
33kg
not 30kg



Which Drugs Do We Use?

HAART = HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY

- Nothing less than **3** drugs
- Usually 2 NRTI's + either NNRTI or PI
- Few new drugs being tested

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Regimens For Children

(DOH Guidelines)

	Less than 3years	>3 years (>10kg)
1st line	stavudine (d4T) lamivudine(3TC) kaletra®	stavudine (d4T) lamivudine(3TC) efavirenz (Stocrin)
2nd line	zidovudine (AZT) didanosine (ddI) efavirenz/NVP	zidovudine (AZT) didanosine(ddI) kaletra®

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)

$$BSA\ (m^2) = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$$

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Antiretroviral Drug Dosing Chart for Children (2007)

Wt. band (kg)	Stavudine (d4T)	Lamivudine (3TC)	Zidovudine (AZT)	Didanosine (ddI)	Abacavir (ABC)	Efavirenz (EFV)	Nevirapine (NVP)		Lopinavir/ Ritonavir (LPV/rtv)	Ritonavir boosting (RTV)	Cotrimox-azole	Multi-vitamins
	Solution 1mg/ml; capsules 15,20,30mg	Solution 10mg/ml; tablets 150mg (scored)	Solution 10mg/ml; capsules 100mg, tablets 300mg (not scored)	Tablets 25,50,100mg (chewable or dispersible in 30ml water)	Solution 20mg/ml tablets 300mg (not scored)	Capsules 50,200mg; tablets 600mg (not scored)	Solution 10mg/ml; tablets 200mg (scored)		Solution 80/20mg/ml; soft capsules 133.3/33.3mg	Solution 80mg/ml	Solution 40/200mg/ 5ml; tablets 400/80mg (scored)	Solution; Vit B Co tablets
	1mg/kg/dose TWICE daily	4mg/kg/dose TWICE daily	180-240mg/m^2/dose TWICE daily	90-120mg/m^2/dose TWICE daily	8mg/kg/dose TWICE daily	By wt. band ONCE daily	160-200mg/m^2/dose * Induction ONCE daily	* Maintenance TWICE daily	230-300mg/m^2/dose LPV TWICE daily	** ONLY as booster for LPV/rtv with Rifampicin TWICE daily	ONCE daily	ONCE daily
<5	Consult with a clinician experienced in paediatric ARV prescribing										2.5ml	2.5ml
5-5.9	6ml	3ml	6ml	2x25mg tabs	2ml	Dosing <10kg not established	6ml	6ml	1ml	**1ml	5ml or ½ tab	
6-6.9	7ml		7ml		3ml		7ml	7ml	1.5ml	**1.2ml		
7-7.9	10mg: disperse contents of 20mg capsule in 5ml water - give 2.5ml	4ml	8ml		4ml		8ml	8ml				
8-8.9			9ml or 1 cap				9ml or ½ tab	9ml or ½ tab				
9-9.9			10ml or 1 cap									
10-10.9	15mg: disperse 15mg capsule contents in 5ml water	5ml		3x25mg tabs am; 2x25mg tabs pm	5ml	200mg cap	10ml or ½ tab	10ml or ½ tab				5ml
11-11.9				3x25mg tabs					2ml	**1.5ml		
12-13.9		6ml or ½ tab	11ml or 1 cap		6ml		11ml or ½ tab	11ml or ½ tab				
14-16.9	20mg: disperse 20mg capsule contents in 5ml water	½ tab	2 caps am; 1 cap pm	2x50mg tabs am; 3x25mg tabs pm	7ml	200mg cap + 50mg cap	½ tab	1 tab am; ½ tab pm			10ml or 1 tab	
17-19.9				2x50mg tabs	8ml		1 tab		2.5ml bd or 2 caps am + 1 cap pm	**2ml		
20-24.9	20mg am; 30mg pm	1 tab am; 1/2 tab pm	2 caps	1x100mg tab + 1x25mg tab	10ml	200mg cap + 2x50mg caps			3ml or 2 caps	**2.5ml		
25-29.9	30mg	1 tab			1 tab	200mg cap + 3x50mg caps		1 tab	3.5ml or 2 caps			
30-34.9			1 tab			2x200mg caps			4ml or 3 caps	**3ml	2 tabs	1 tab
35-39.9									5ml or 3 caps	**3.8ml		
>40						600mg tab						

* 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.

Body Surface Area (BSA) $m^2 = \sqrt{\frac{\text{Mass (kg)} \times \text{Height (cm)}}{3600}}$

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

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Viral Load

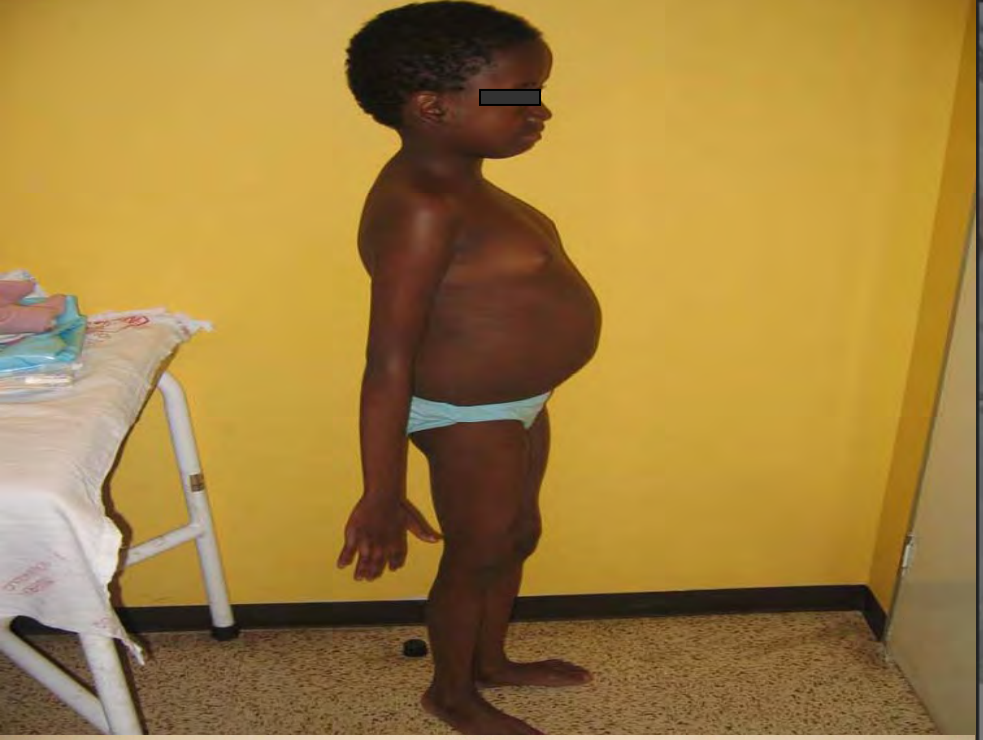
- One log drop by 4 weeks
- Undetectable by 24 weeks(<50)
- Thereafter every 6 months
- Viral blips
- If above 1000 copies/ml confirm with a second test. Increase adherence counseling.

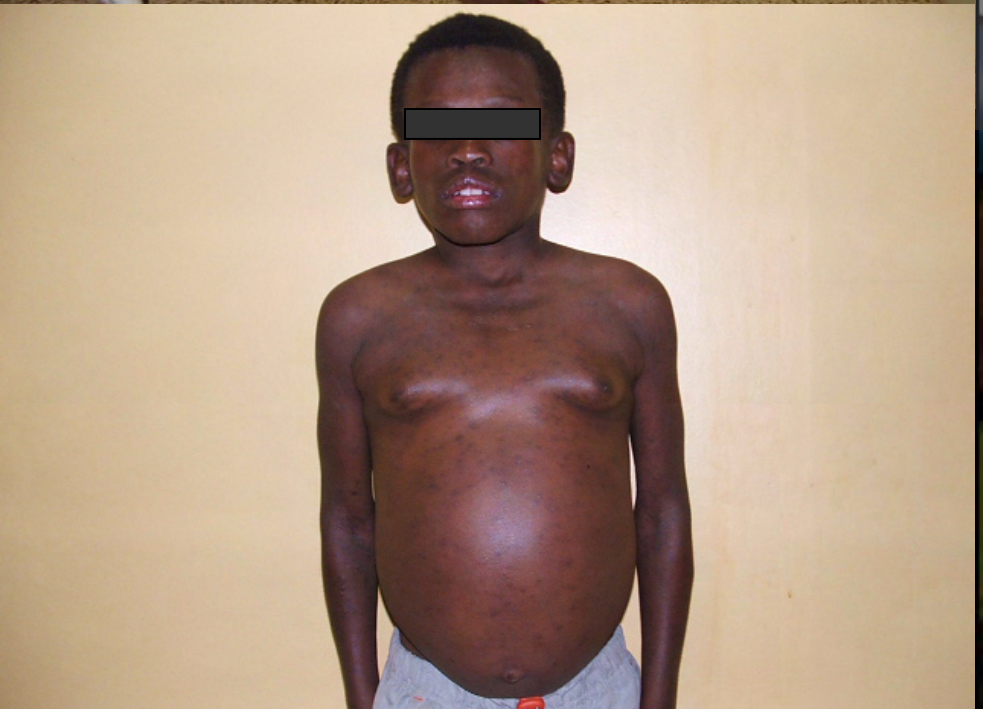
Side Effects (Adverse Events)

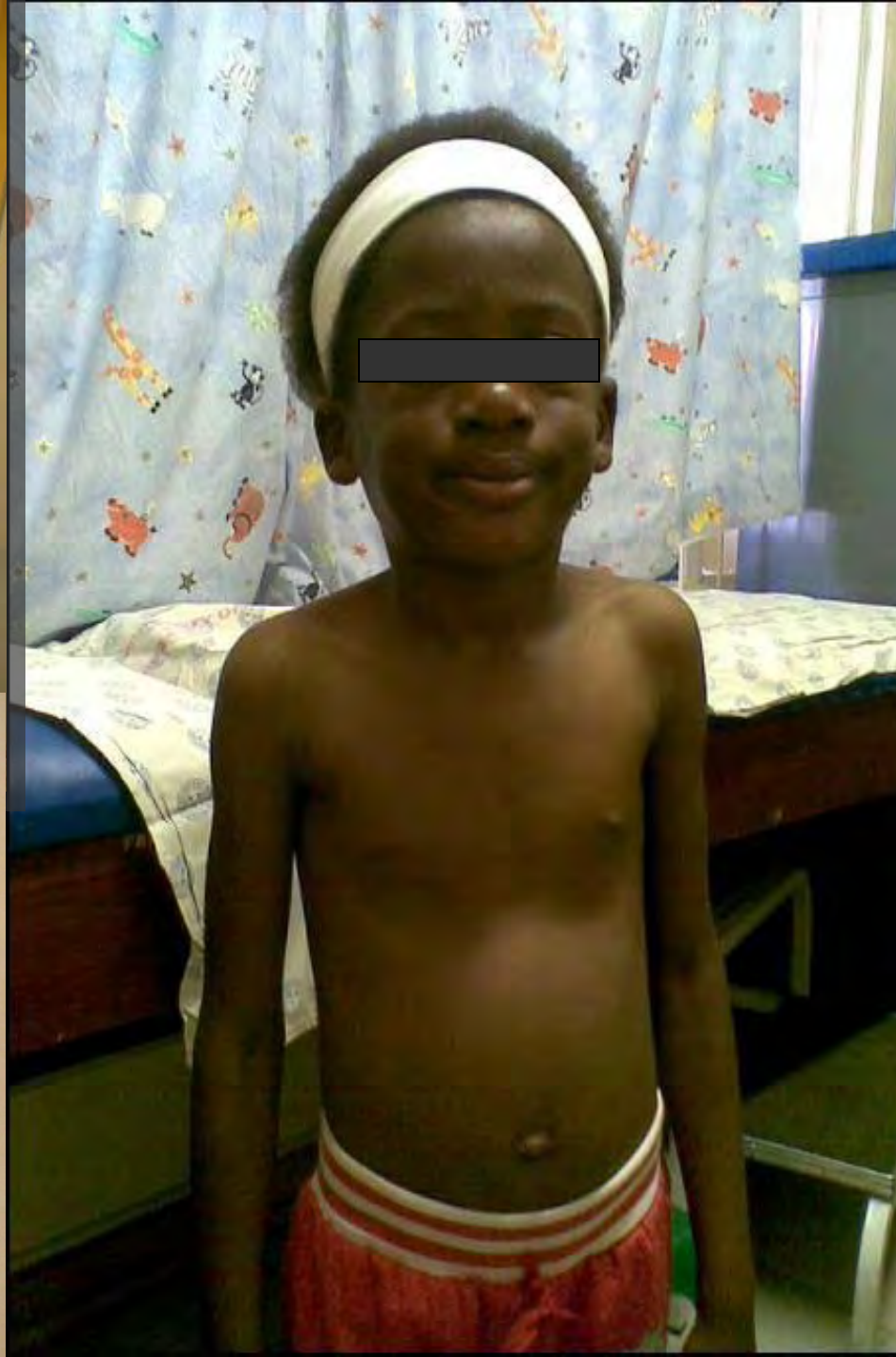
- In general, side effects are less common in children
- Same spectrum of side effects that occur in adults reported in children.
  - Some are rare in children, e.g. NVP-related symptomatic hepatotoxicity
  - Some are more common, e.g. NVP and EFV-related rash
  - Some occur only in children, e.g. Tenofovir-related loss of bone density

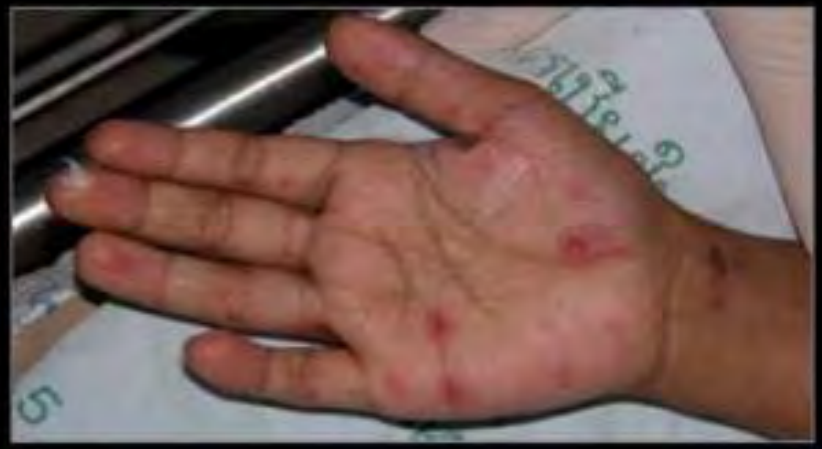
Side Effects (Adverse Events)

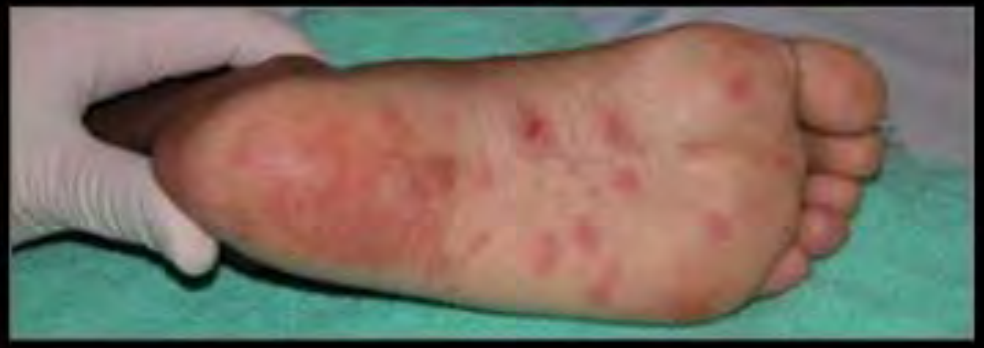
- Complications of HIV and toxicity to other drugs can look like ARV-related side effects.
- Always consider these too.
  - HIV Hepatitis
  - hepatitis A, B,C, other viruses eg. CMV, EBV
  - INH
  - Anaemia
  - malaria
  - Viral Exanthem
  - Cotrimoxazole

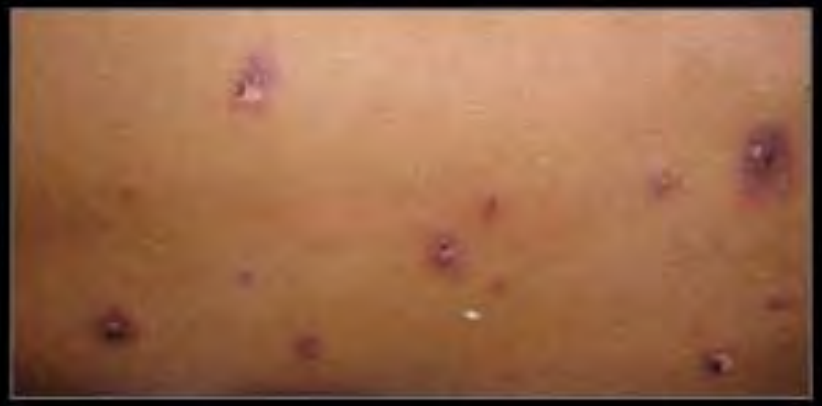












11 days after starting HAART containing nevirapine, this 11 year old boy presented with Stevens-Johnson syndrome. Liver toxicity is often also present, though not in this case. For more details, see http://www.med.cmu.ac.th/dept/pediatrics/06-interest-cases/ic-74/page1.htm

Picture credit: Dr. V. Sirisanthana

Assistance for Children who don't Qualify for HAART

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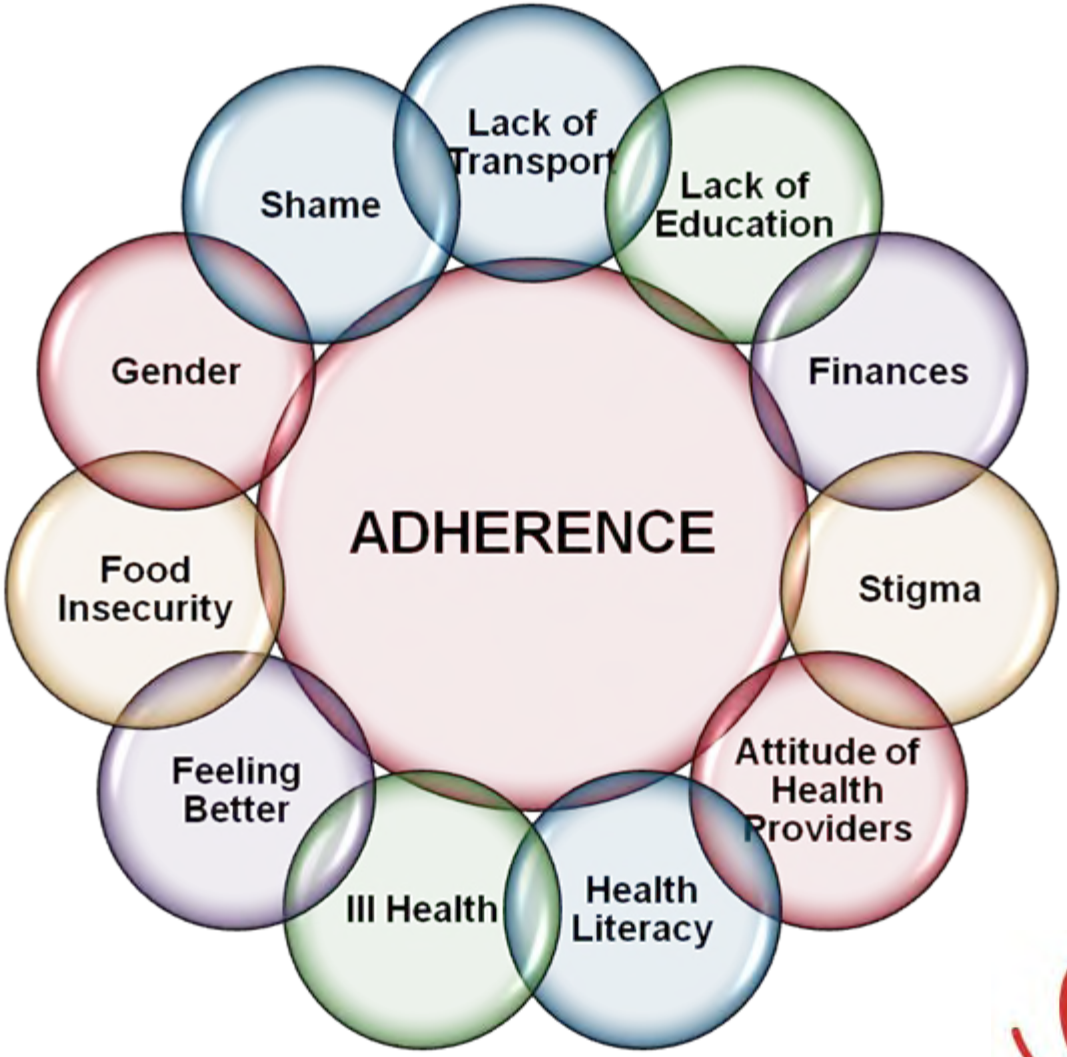
Factors Affecting Adherence



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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 (ddI)
- 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.

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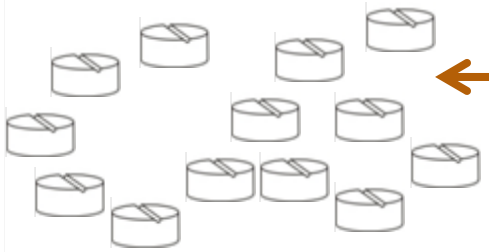
Drug Interactions

Enzyme System Inhibitors / Inducers

rifampicin
efavirenz
nevirapine
phenytoin
St John's wort
garlic

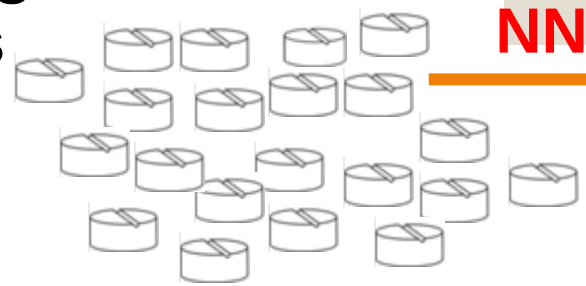


Metabolism

Enzyme system CYP450

PIs
NNRTIs

Enzyme System Inhibitors
Enzyme System Inducers



ritonavir
saquinavir
indinavir
nelfinavir
grapefruit juice
ketoconazole

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TB Rx and Kaletra

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

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When To Change Treatment

- **Toxicity**
  - Short-term side-effects
  - Longterm 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

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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……

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CHAIN OF SURVIVAL

EARLY ACCESS

EARLY CPR

EARLY DEFIBRILLATION

EARLY ADVANCED CARE


CHAIN OF
SURVIVAL
EARLY ACCESS
EARLY CPR
EARLY DEFIBRILLATION
EARLY ADVANCED CARE
PCR
STAGING
HARTC

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).

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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.

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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 ?

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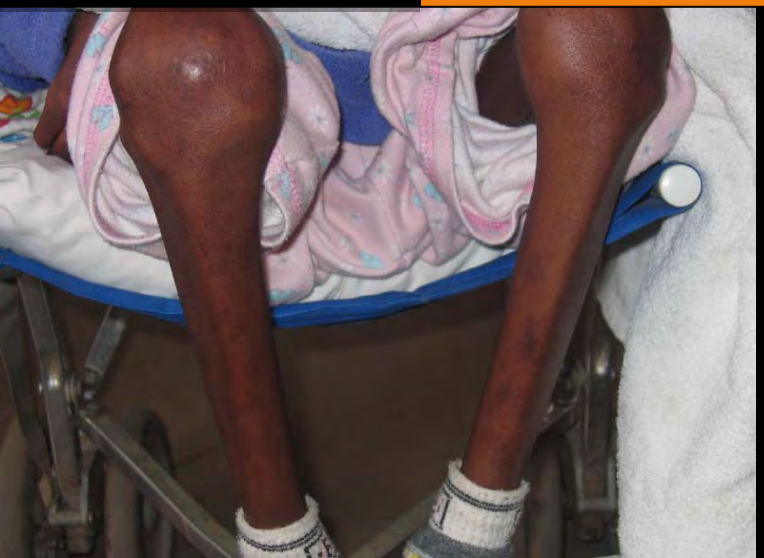
Before and After ART

6 Months Later

Before and After ART

BEFORE



6 weeks later