

# Treatment Failure in Children

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# Learning Objectives

1. Define and examine definitions for antiretroviral treatment failure
2. Identify antiretroviral treatment failure in children
3. Identify reasons for pediatric treatment failure
4. Formulate site support approaches for monitoring detection and management of treatment failure.

# Case EM

- Born to Mother in PMTCT given sd-NVP no prophylaxis given to infant
- 6wk: began CTX
- 3mo: thrush cough, wt <10<sup>th</sup>%=WHO stage III, CD4=1126(22%),
- After nutrition and adherence counseling began ZDV+3TC+NVP.

# EM continued

- 6 mo: defaulted for 2 mo due to traveling
- 8 mo: re-appeared with wt decline  $<5^{\text{th}}\%$ , adherence re-emphasized and ARV continued.
- 9 mo: admitted with gastroenteritis + dehydration, CD4=300
- 13 mo: re-admitted for gastroenteritis+dehydration, bilateral hilar adenopathy on CXR, CD4=297
- Pt referred for TB treatment

# Defining Treatment Failure

- It is anticipated that at some point in time ART may fail, as evidenced by clinical, immunologic, or virologic progression
  - **Clinical:** Progression of symptoms and signs, advancing WHO stage
  - **Immunologic:** CD4+ count falling/failing to rise
  - **Virologic:** Detectable, rising viral load and subsequent development of resistance mutations

# Treatment failure in children-clinical criteria

- Treatment failure should be considered:
  - New or recurrent class 3 or 4 clinical event in a child on therapy for a minimum of 6 months
- Distinguish clinical treatment failure from IRIS.
- Assess children with growth failure (stage 3 or 4) for dietary deficiencies or other treatable causes of malnutrition.
- In endemic areas, PTB may not indicate treatment failure.

# WHO Stage 3

- *Unexplained* moderate malnutrition ( $-2SD$  or Z score wt for age) not responding to standard therapy
- *Unexplained* persistent diarrhoea ( $>14$  days)
- *Unexplained* persistent fever (intermittent or constant,  $> 1$ mo)
- Oral candidiasis (outside neonatal period)
- Oral hairy Leukoplakia
- Pulmonary tuberculosis
- Severe recurrent presumed bacterial pneumonia ( $>2$  episodes/12 months)
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymphoid interstitial pneumonitis (LIP)
- *Unexplained* anaemia ( $<8g/dL$ ), neutropenia ( $<1000/mm^3$ ), or thrombocytopenia ( $<30,000/mm^3$ ) for  $>1$  mo.
- HIV-related cardiomyopathy
- HIV-related nephropathy

# WHO Stage 4

- *Unexplained* severe wasting or severe malnutrition ( $-3$  SD or Z score wt for age ) not responding to standard therapy
- Encephalopathy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections ( $>2$  episodes/12 months, *excluding* pneumonia)
- Chronic orolabial or cutaneous HSV (lasting  $> 1$  mo)
- Extra-pulmonary tuberculosis
- Kaposi's sarcoma
- Oesophageal candidiasis
- CNS toxoplasmosis
- Cryptococcal meningitis
- Any disseminated endemic mycosis
- Cryptosporidiosis or Isosporiasis (with diarrhoea  $> 1$  month)
- CMV infection of organ other than liver, spleen, lymph nodes (and onset age  $>1$  month)
- Disseminated mycobacterial disease other than tuberculosis
- ETC.

# WHO CD4 criteria for treatment failure‡

- Age-related severe immunodeficiency after initial immune recovery .
- New progressive age related severe immunodeficiency, if confirmed (esp. if “critical”).
- Rapid decline to severe immunodeficiency (esp if “critical”).

<b>Age related severe immunodeficiency</b>	<b>“Critical” values for immunodeficiency</b>
<11m (<25% or <1500)	
12-35 (<20% or <750)	<15%
36-59 (<15% or <350)	<10%
≥5 yr (<15% or <200)	<10% (<100)

‡ At least 6 months of treatment and adherence is adequate

# Treatment Failure: Major Causes

1. Non adherence
2. Non adherence
3. Non adherence
4. Incorrect dosage- failure to adjust for growth
5. Acquired or pre-existing resistance

# New clinical event: none or new stage 1 or 2 event

- Manage illness or condition.
- Repeat CD4 .
- Address adherence
- Increase frequency of visits and CD4 monitoring if CD4 is declining.
- Consider switching regimen *only if* CD4 measures are below age-related severe immunodeficiency threshold

# New clinical event: stage 3\*

- Manage illness or condition.
- Repeat CD4.
- Switch to new regimen if CD4 is below age-related threshold for severe immunodeficiency.
- Increase frequency of visits and CD4 monitoring if CD4 is declining.

\*If event is growth failure assess for treatable causes, PTB may not indicate disease progression

# Clinical event:new stage 4

- Manage as for new stage 3 except:
  - Switching regimen is recommended

# Minimal system requirements

## 1. Clinical failure

### Staging

- Capacity/competency for proper growth monitoring
- Capacity/competency for neurodevelopmental assessment

## 2. Immunologic failure

Capacity for reliable timely CD4 monitoring

Competency in interpretation

## 3. Competency in assessing and supporting adherence

ICAP Standards of Care (SOC) for Pediatrics		Quarterly Measure of SOC	Denominator	Possible Source of information	Result of Quarterly measure of SOC		
					Possible Actions		
<b>HIV-Infected Children</b>							
1	All HIV-infected children with disease progression should be assessed for treatment failure	Proportion of HIV-infected children with treatment failure who had recognition and appropriate assessment	# of HIV-infected children with treatment failure and it was addressed	Pediatric charts	<75%	75-94%	≥95%
			# of children with decline in clinical stage		Evaluate this month	Prioritize and evaluate next quarter	On target
2	All HIV-infected children with decline in CD4 should be assessed for treatment failure	Proportion of HIV-infected children with treatment failure who had recognition and appropriate assessment	# of HIV-infected children with treatment failure and it was addressed	Pediatric charts			
			# of children with decline in CD4		Evaluate this month	Prioritize and evaluate next quarter	On target
3							
4	All HIV-infected children should have TB screening at their first visit and at least every 6 months thereafter	% of HIV-infected children screened at enrollment each quarter	# of patients enrolled in the past quarter screened for TB at enrollment	Pediatric charts			
			# of patients enrolled in the past quarter		Evaluate this month	Prioritize and evaluate next quarter	On target
5	All HIV patients with active TB and TB patients diagnosed with HIV should receive cotrimoxazole prophylaxis.	% of HIV-infected children with active TB on CTX prophylaxis	# of children with active TB on CTX				
			# of HIV patients with active TB		Evaluate this month	Prioritize and evaluate next quarter	On target
6	All HIV-infected children newly enrolled in care should complete a baseline psychosocial assessment that includes a follow-up plan for additional support needs	% of HIV-infected children with completed baseline psychosocial assessment and follow-up plan	# of newly enrolled pediatric patients with a completed psychosocial assessment and follow-up plan	Pediatric chart			
			# of pediatric patients newly enrolled in HIV care		Evaluate this month	Prioritize and evaluate next quarter	On target
7	All HIV-infected children on ART should be assessed for adherence to treatment at each follow-up clinic visit (non-pharmacy).	% of HIV-infected children on ART assessed for adherence to care and treatment at a follow-up visit	# of HIV-infected children on ART seen in qtr assessed for adherence to treatment	Pediatric charts			
			# of HIV-infected children on ART seen for a follow-up visit in qtr		Evaluate this month	Prioritize and evaluate next quarter	On target
8	All HIV-infected children should be counseled on adherence to care and treatment at every follow-up clinic visit. (review)	% of HIV-infected children seen with at least one* counseling session that addresses adherence to care and treatment	# of HIV-infected children seen for follow-up in qtr with ≥1 counseling session that addresses adherence to care and treatment	Pediatric charts			
			# of HIV-infected children seen for follow-up visit in qtr		Evaluate this month	Prioritize and evaluate next quarter	On target

**Complete the following if the patient has been on treatment for at least 6 months.**

**1. All HIV-infected children with disease progression or decline in CD4 should be assessed for treatment failure.**

**Treatment failure should be considered in children who are receiving HAART and have worsening WHO stage and/or decline in CD4 % and/ or incomplete immunologic response.**

**1a. Has the child been on HAART for  $\geq 1$  year**

- Yes: Continue with next question
- No: END

**If the child has been receiving HAART for  $\geq 1$  year, answer the following questions:**

**1b. Disease progression**

**Has the WHO stage worsened?**

- Yes: Treatment failure was considered because of decline in WHO clinical stage from \_\_\_\_\_ to \_\_\_\_\_.
- No: It is the same .

**1c. Immunologic decline**

**Has the CD4 % or absolute declined to pre-therapy baseline level?**

- Yes: CD4 fell from \_\_\_\_\_ (pre ART) to \_\_\_\_\_ on ART.
- No

**Has the CD4 declined by 5% points (if < 6 years ) or \_\_\_\_\_ (if > 6 years)**

- Yes: CD4 has fallen by \_\_\_\_\_ since initiation of HAART.
- No

**1d. Incomplete immunologic response**

**Has CD4 failed to increase by 5% (if < 6 years of age) or increase by 50cells/mm (if > 6 years of age) since initiation of ART?**

- Yes: CD4 has increased by \_\_\_\_\_ since initiation of ART.

**If NO to all to all of the above, END.**

**If yes to any of the above, answer next question**

**1e. Is there documentation in the medical record that treatment failure was considered and addressed? (e.g. adherence evaluation, CD4 repeated , change in HAART regimen)**

- Yes: treatment failure was addressed by ordering repeat CD4 in < 6 months
- Yes: treatment failure was addressed by evaluating adherence
- Yes: treatment failure was addressed by changing or making a plan to change HAART regimen
- No: there was no documentation of recognition of treatment failure