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Antiretroviral Management in the Pediatric Population

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Objectives

- Describe the basic components of pharmaceutical care as it applies to pediatric HIV/AIDS care
- Interpret laboratory and diagnostic data for regimen selection and monitoring of safety and efficacy of ARV therapy
- Discriminate regimens and doses used for different age groups
- Explain the clinical toxicology of antiretrovirals (ARVs) in pediatrics

Epidemiology in Ethiopia



- Currently 134,586 children under 14 years living with HIV/AIDS in Ethiopia
- Probably more than half of these children (67,000) require ARVs, but only 4863 (~7%) were receiving ARVs as of March 2008
- Without treatment, 75% of these children will die before age 5
- >90% of children acquire HIV from their mothers
- <10% of HIV-infected pregnant women in sub-Saharan Africa receive any form of prevention of mother-to-child transmission (PMTCT)

Diagnosis of HIV in Infants



- Preferred virologic assays: HIV DNA PCR and HIV RNA assays
 - Infants <18 months require virologic assays that directly detect HIV to diagnose HIV infection
 - Antibody assays cannot be used due to the persistence of maternal HIV antibody
 - Dried blood spots (DBS) for DNA PCR
 - Used in newborn screening programs
 - Does not require venipuncture, obtained by heel-prick
 - Stored at room temperature, easily transported to central sites for testing

Diagnosis of HIV in Infants (Ethiopia Guidelines)



■ Virologic Testing Available

- DNA PCR at 6 weeks, start cotrimoxazole prophylaxis
 - (+) PCR, start HAART
 - (-) PCR, follow and continue cotrimoxazole prophylaxis
- Rapid antibody test at ≥ 12 months age or at least 6 weeks after cessation of breastfeeding
 - (+) antibody, start HAART
 - (-) antibody, HIV-negative

■ NO Virologic Testing

- Start cotrimoxazole prophylaxis at 6 weeks, use WHO criteria for presumptive diagnosis of HIV
 - Eligible for HAART – start therapy
 - Not eligible – follow and continue cotrimoxazole prophylaxis
- Rapid antibody test at ≥ 18 months age or at least 6 weeks after cessation of breastfeeding
 - (+) antibody, start HAART
 - (-) antibody, HIV-negative

WHO criteria for presumptive diagnosis of HIV in <18 month olds

- A presumptive diagnosis of severe HIV disease should be made if:
 - The infant is confirmed HIV antibody positive; and
 - Diagnosis of any AIDS-indicator condition(s) can be made; or
 - The infant is symptomatic with two or more of the following:
 - Oral thrush
 - Severe pneumonia
 - Severe sepsis
- Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include:
 - Recent HIV-related maternal death; or advanced HIV disease in the mother
 - **CD4 <20% in infant**

Laboratory Monitoring of Pediatric HIV Infection



- For children <5 years old, **CD4 percentage** is preferred for monitoring immune status because of age-related changes in absolute CD4 count
- CD4 percentage/count and plasma HIV RNA
 - Measured at the time of diagnosis of HIV infection and **at least every 3–4 months**
 - More frequent monitoring if <6–12 months old, suspected deterioration, or when initiating or changing therapy
- **Goal of antiretroviral therapy = reduce plasma HIV RNA levels to below the limits of detection AND to prevent AIDS progression / death**

When to Initiate Therapy in ARV naïve Children

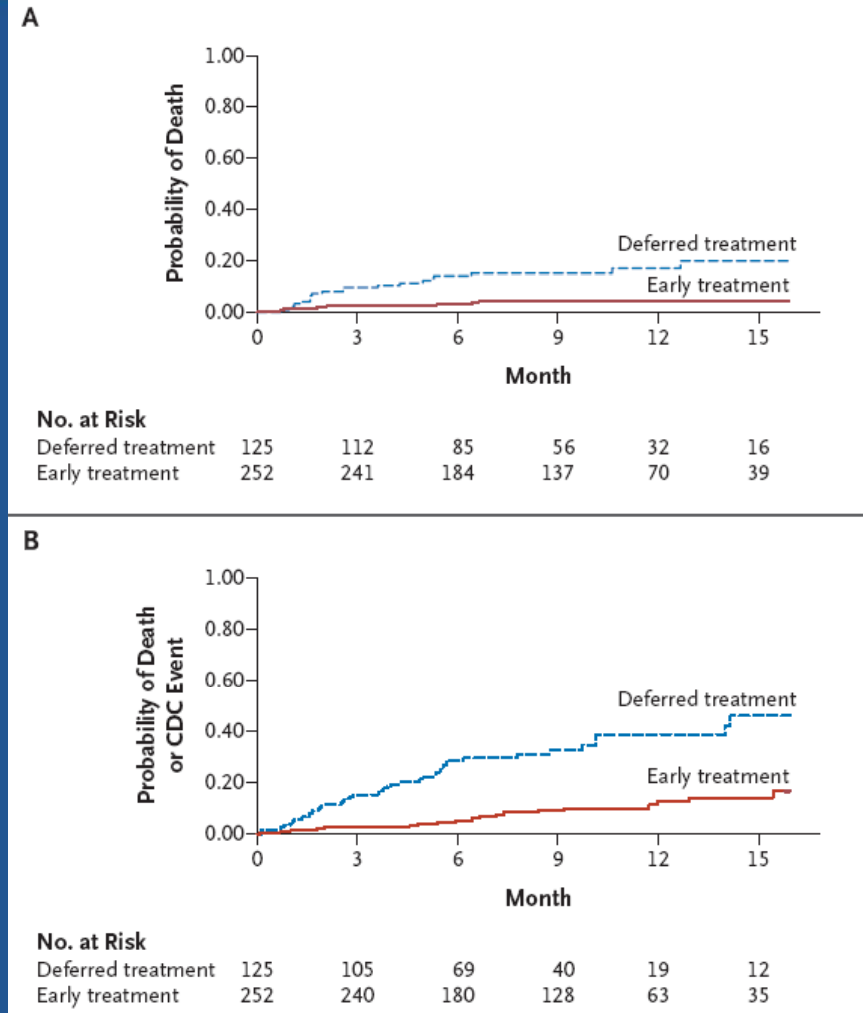
- Infants < 12 months should receive HAART regardless of CD4 count
- Infants ≥ 12 months:
 - Follow WHO pediatric clinical stage of disease and CD4 value to determine need for HAART

Age-related CD4 values

Classification of HIV-associated immunodeficiency	<11 months	12-35 months	36-59 months	≥5 years
Not significant	>35%	>30%	>25%	>500 cells/mm ³
Mild	30-35%	25-30%	20-25%	350-499
Advanced	25-30%	20-25%	15-20%	200-349
Severe	<25%	<20%	<15%	<200

ARV-naïve HIV-Infected Infants <12 months

- Children with HIV Early Antiretroviral Therapy [CHER] study:
 - South African clinical trial: initiation of HAART prior to age 12 weeks in asymptomatic infants with CD4 >25% vs. delayed HAART
 - 75% reduction in early mortality found with early initiation
 - 20/125 (16%) in the deferred-therapy group died vs. 10/252 (4%) in the early-therapy group, $P < 0.001$



WHO Recommendations for Initiating ARV in Children \geq 12 months



Clinical Stage	Immunologic Marker	Recommendation
Stage 4	All CD4 counts	Treat
Stage 3	CD4 available	Treat <ul style="list-style-type: none"> Can defer in children with TB, LIP, OHL, or thrombocytopenia if only mild immunodeficiency
	No CD4	Treat
Stage 2	CD4 available	Treat if CD4: <ul style="list-style-type: none"> < 20% or < 750 cells/mm³ for child 12-35 months < 20% or < 350 cells/mm³ for child 36-59 months < 15% or < 200 cells/mm³ for child >5 years
	No CD4	Treat if TLC: <ul style="list-style-type: none"> < 3000 cells/mm³ for child 12-35 months < 2500 cells/mm³ for child 36-59 months < 2000 cells/mm³ for child 5-8 years
Stage 1	CD4 available	Treat if CD4: <ul style="list-style-type: none"> < 20% or < 750 cells/mm³ for child 12-35 months < 20% or < 350 cells/mm³ for child 36-59 months < 15% or < 200 cells/mm³ for child >5 years
	No CD4	DO NOT treat

DHHS Recommendations for Initiating ARV in Pediatric Patients



Age	Criteria	Recommendation
<12 months	Regardless of clinical symptoms, immune status, or viral load	TREAT
1–<5 years	<ul style="list-style-type: none"> ▪ AIDS or significant HIV-related symptoms ▪ CD4 <25%, regardless of symptoms or HIV RNA level ▪ Asymptomatic or mild symptoms and <ul style="list-style-type: none"> ▪ CD4 \geq25% and ▪ HIV RNA \geq100,000 copies/mL ▪ Asymptomatic or mild symptoms and <ul style="list-style-type: none"> ▪ CD4 \geq25% and ▪ HIV RNA <100,000 copies/mL 	<ul style="list-style-type: none"> ▪ TREAT ▪ TREAT ▪ Consider ▪ Defer
\geq 5 years	<ul style="list-style-type: none"> ▪ AIDS or significant HIV-related symptoms ▪ CD4 <350 cells/mm³ ▪ Asymptomatic or mild symptoms and <ul style="list-style-type: none"> ▪ CD4 \geq350 cells/mm³ and ▪ HIV RNA \geq100,000 copies/mL ▪ Asymptomatic or mild symptoms and <ul style="list-style-type: none"> ▪ CD4 \geq350 cells/mm³ and ▪ HIV RNA <100,000 copies/mL 	<ul style="list-style-type: none"> ▪ TREAT ▪ TREAT ▪ Consider ▪ Defer

DHHS Recommendations for Monitoring ARV Therapy in Pediatrics



Time After Starting Therapy	Toxicity Monitoring	Adherence and Efficacy Monitoring
Baseline (Prior to Initiation of Therapy)	<ul style="list-style-type: none"> Clinical history Complete blood count with differential Blood chemistries 	<ul style="list-style-type: none"> CD4 cell count/percentage HIV RNA level (if available)
1-2 weeks	<ul style="list-style-type: none"> Clinical history 	<ul style="list-style-type: none"> Adherence screen
4-8 weeks	<ul style="list-style-type: none"> Clinical history Complete blood count with differential Blood chemistries 	<ul style="list-style-type: none"> Adherence screen CD4 cell count/percentage HIV RNA level (if available)
Every 3-4 months	<ul style="list-style-type: none"> Clinical history Complete blood count with differential Blood chemistries 	<ul style="list-style-type: none"> Adherence screen CD4 cell count/percentage HIV RNA level (if available)
Every 6-12 months	<ul style="list-style-type: none"> Lipid Panel 	

What Drugs to Start

- Combination therapy with at least 3 drugs, including either a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) plus a dual nucleoside analogue reverse transcriptase inhibitor backbone (NRTI)
- Infants identified during 1st 6 weeks of life while receiving zidovudine chemoprophylaxis should have zidovudine discontinued and initiate combination therapy
- Antiretroviral drug resistance testing is recommended prior to initiation of therapy in all treatment-naïve children (if available)

Ethiopia Guidelines: Initial Antiretroviral Regimens



Preferred Regimen
Children 1-3 years old
d4T + 3TC + NVP
OR
AZT + 3TC + NVP

Preferred Regimen
Children ≥ 3 years old
d4T + 3TC + (NVP or EFV)
OR
AZT + 3TC + (NVP or EFV)

Infants up to 12 months no
history of PMTCT or NNRTI
exposure

d4T + 3TC + NVP
OR
AZT + 3TC + NVP

Infants up to 12 months with
history of PMTCT or NNRTI
exposure

d4T + 3TC + LPV/r
OR
AZT + 3TC + LPV/r

DHHS Recommended Initial Antiretroviral Regimens



Preferred Regimen

Alternative Regimen

NNRTI-based

- EFV (≥ 3 years old)
- NVP (< 3 years old or can't swallow capsules)

- NVP (≥ 3 years old)

PI-based

- LPV/r

- ATV/r (≥ 6 years old)
- FPV/r (≥ 6 years old)
- NFV (≥ 2 years old)

NRTI backbone options

- ABC + (3TC/FTC)
- AZT + (3TC/FTC)
- ddI + FTC
- TDF + (3TC/FTC) (for Tanner Stage 4 or post-pubertal adolescents only)

- ABC + AZT
- AZT + ddI
- d4T + (3TC/FTC)

Pediatric Triple-fixed Dose Combinations (FDC)

Easier to manufacture, transport, store and dispense

More accurate dosing compared to measuring syrups and more palatable

Improved adherence

- Triple FDC:
 - Triomune Baby: d4T (6mg) / 3TC (30mg) / NVP (50mg)
 - Triomune Junior: d4T (12mg) / 3TC (60mg) / NVP (100mg)
- Dual FDC:
 - Lamivir-S Baby: d4T (6mg) / 3TC (30mg)
 - Lamivir-S Junior: d4T (12mg) / 3TC (60mg)

Pediatric Dual FDC Combinations and Lead-in Dosing



- **Initiation of NVP-based HAART in naïve patients**
 - Requires a lead-in period: 2 weeks of NVP once daily
 - Minimizes the risk of NVP related rash
 - After 2 weeks, dose escalation to NVP twice daily
- **Dual pediatric FDC products**
 - **Contain d4T+3TC only**
 - Combine with once daily NVP during lead-in period
 - May also combine with EFV or PIs in alternative regimens
- **Triple FDC in the mornings and a dual FDC (d4T and 3TC) in the evenings followed by the use of Triple FDC twice a day thereafter**

Pediatric Dosing of First Line ARVs



Weight (Kg)	Maintenance Dose			Lead-in Period Formulation and Dosing			
	Triple FDC Triomune	AM	PM	Triple FDC Triomune	AM	Dual FDC Lamivir-S	PM
3-5.9	Triomune Baby	1	1	Triomune Baby	1	Lamivir-S Baby	1
6-9.9	Triomune Baby	1.5	1.5	Triomune Baby	1.5	Lamivir-S Baby	1.5
10-13.9	Triomune Baby	2	2	Triomune Baby	2	Lamivir-S Baby	2
14-19.9	Triomune Junior	1.5	1	Triomune Junior	1.5	Lamivir-S Junior	1
20-24.9	Triomune Junior	1.5	1.5	Triomune Junior	1.5	Lamivir-S Junior	1.5
25-34.9	Adult FDC 30/150/200	1	1	Adult FDC	1	Adult Dual FDC	1

Dosing Issues with fixed combinations of ARVs



- Fixed amounts of drug dosed by weight band (risk underdosing and overdosing at extremes of weight band)
- Acceptable dose **ranges** were established:
 - Lower limit = currently acceptable dose
 - Upper limit = 25% above currently acceptable dose
- Example:
 - 24 kg patient taking Triomune Junior (**d4T 12mg / 3TC 60mg / NVP 100mg**) 1.5 tabs twice daily
 - Standard dose for d4T = 1mg/kg/dose = 24 mg twice daily
 - Patient is currently receiving 12mg x 1.5 = 18 mg twice daily
 - Underdosing should be avoided whenever possible

Advantages / Disadvantages of NNRTI Options

Advantages

Disadvantages

Efavirenz (EFV)

≥3 years old

- Potent antiretroviral activity
- Once daily
- Can give with food

- Neuropsychiatric side effects
- Rash
- No commercially available liquid
- No data for dosing in children <3 years old
- Teratogenic in 1st trimester

Nevirapine (NVP)

<3 years old

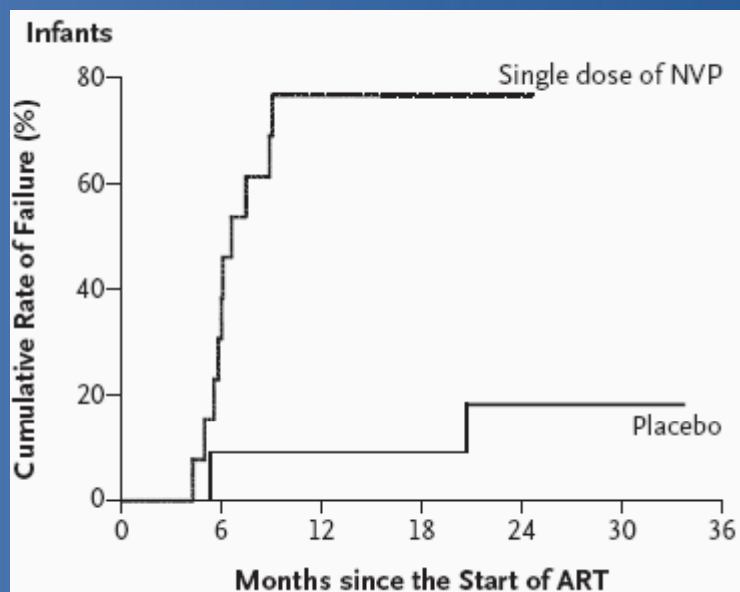
- Liquid formulations available
- Dosing information for younger infants available
- Can give with food

- Higher incidence of rash / hypersensitivity reaction
- Higher rates of serious hepatotoxicity in adults

Efficacy of NVP based ARV in Infants Exposed to single dose NVP



- 15 SD-NVP exposed and 15 unexposed infants were initiated on NVP-based therapy at a mean age of 8 months (range 2–33 months)¹
- 34% vs. 91% had viral load <400 copies/mL, respectively¹
- 44 SD-NVP exposed vs. 48 unexposed started NVP-based therapy at an older age of 1.6 years²
- No difference in response between 2 groups²
- A larger randomized control clinical trial (P1060) is designed to address the impact of NVP exposure during PMTCT on the efficacy of NVP based therapy in infants 3 months to 3 years old



1. Lockman et al. NEJM 2007;356:135-47.

2. Barlow-Mosha et al. CROI 2008. Abstract 583.

LPV/r Pediatric Dosing Studies

- LPV/r well studied in pediatric patients but dosing is controversial:
 - Doses directly scaled for BSA: 400/100mg adult dose \sim 230/57.5mg per m² of BSA
 - Pediatric PK studies found that the 230/57.5mg per m² of BSA dose only produces C_{trough} that is 76% of the adult value (4.74 vs. 7.1 mcg/mL)¹
 - LPV/r 300/75mg/m² BSA dose produced C_{trough} 7.91 mcg/mL¹
 - Therefore in children 6 months – 12years old, some clinicians choose to use the higher dose of **LPV/r 300/75mg/m² BSA** (especially when NVP co-administered)²
 - Children <6 months had even lower troughs when given the higher dose^{3,4}

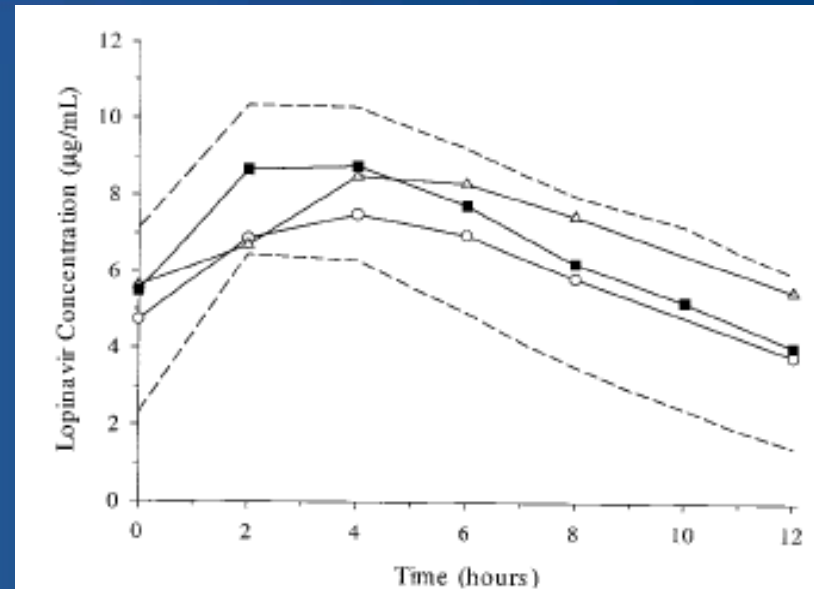


FIG. 2. Mean 12-h lopinavir concentration profiles for pediatric subjects receiving the higher lopinavir/ritonavir dose (300/75 mg/m² BID, Δ) in the presence of nevirapine and those receiving the lower dose (230/57.5 mg/m² BID, \circ) in the absence of nevirapine. Also shown is the mean 12-h lopinavir concentration profile (400/100 mg BID, \blacksquare) observed in a previous Phase II adult study ($n = 21$).⁸ - - - -, interquartile range of the adult concentrations. Average lopinavir C_{predose} levels for both dosing regimens are well above (i.e. >60-fold) the protein binding-adjusted 50% inhibitory concentration for wild-type HIV ($\sim 0.07 \mu\text{g/ml}$).¹¹

1. Verweel et al. Antivir Ther 2007;12(4):453-8.

2. Saez-Llorens et al. PID 2003;22(3):216-24.

3. Chadwick et al. AIDS 2008;22(2):249-55.

4. Pinto et al. CROI 2007. Abstract 716.

Advantages / Disadvantages of NRTI Options

Advantages

Disadvantages

d4T plus 3TC/FTC

- Moderate pediatric experience
- Pediatric co-formulations available in Ethiopia
- Can give with food

- d4T higher incidence of lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia

AZT plus 3TC/FTC

- Extensive pediatric experience
- AZT/3TC (Combivir® co-formulation for older children)
- Palatable liquid formulations
- Can give with food

- Bone marrow suppression with AZT

Management of Medication Toxicity / Intolerance



First line drug	Toxicity / Intolerance	Substitution
ABC	<ul style="list-style-type: none"> ▪ Hypersensitivity reaction 	<ul style="list-style-type: none"> ▪ AZT
AZT	<ul style="list-style-type: none"> ▪ Severe anemia / neutropenia ▪ Lactic acidosis ▪ Severe GI intolerance 	<ul style="list-style-type: none"> ▪ d4T or ABC ▪ ABC ▪ d4T or ABC
d4T	<ul style="list-style-type: none"> ▪ Lactic acidosis ▪ Peripheral neuropathy ▪ Pancreatitis ▪ Lipoatrophy / metabolic syndrome 	<ul style="list-style-type: none"> ▪ ABC ▪ AZT or ABC ▪ AZT or ABC ▪ AZT or ABC
EFV	<ul style="list-style-type: none"> ▪ Persistent and severe CNS toxicity ▪ Potential teratogenicity 	<ul style="list-style-type: none"> ▪ NVP ▪ NVP
NVP	<ul style="list-style-type: none"> ▪ Acute symptomatic hepatitis ▪ Hypersensitivity reaction ▪ Severe life threatening rash (Stevens Johnson) 	<ul style="list-style-type: none"> ▪ Triple NRTI or PI-based regimen (DO NOT challenge with EFV)

Definitions of Antiretroviral Treatment Failure



- **Clinical Failure**
 - Decline in growth rate (WHO clinical stage 3 or 4; moderate or severe unexplained malnutrition)
 - Loss of neurodevelopmental milestones or development of HIV encephalopathy
 - Occurrence of new OI or malignancies; recurrence of infections such as oral candidiasis that is refractory to treatment or esophageal candidiasis
- **Immunological Failure**
 - Development of age-related severe immunodeficiency after initial immune recovery
 - Development of new age-related severe immunodeficiency, confirmed with at least one subsequent CD4 measurement
 - Rapid rate of decline to at or below threshold of age-related severe immunodeficiency

Ethiopia Guidelines: Second Line Agents



First Line Regimen

d4T + 3TC + (NVP or EFV)
OR
AZT + 3TC + (NVP or EFV)

d4T + 3TC + LPV/r
OR
AZT + 3TC + LPV/r

Second Line Regimen

ddI + ABC + LPV/r

Consult specialist for
construction of 2nd line
regimen

Ethiopia Guidelines: When to Switch Regimens



Clinical Stage	Availability of CD4	Management Options
New or recurrent T1 and T2 event	<ul style="list-style-type: none">No CD4CD4 available	<ul style="list-style-type: none">DO NOT switchConsider switching regimen only if 2 or more values below age-related threshold or severe immunodeficiency
New or recurrent T3 event	<ul style="list-style-type: none">No CD4CD4 available	<ul style="list-style-type: none">CONSIDER switching regimenSwitching regimen is recommended if CD4 is at or below age-related threshold for severe immunodeficiency* and particularly if child initially had good immune response to ARVs
New or Recurrent T4 event	<ul style="list-style-type: none">No CD4CD4 available	<ul style="list-style-type: none">RECOMMEND switching regimenSwitching is generally recommended but may not be necessary where CD4 is above age-related threshold for severe immunodeficiency

*switching should particularly be considered if values are <15% (12-35 months of age), <10% (36-59 months of age), <100 cells/mm³ (≥5 years of age)



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