

Pocket Guide

2006
DRAFT



Pediatric HIV/AIDS Care & Treatment

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ICAP
Columbia University
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The International Center for AIDS Care &
Treatment Programs (ICAP)
Columbia University Mailman School of Public Health

WHO recently developed revised guidelines on pediatric HIV/AIDS care and treatment, currently available in draft form only at www.who.int/hiv/paediatric/en/index.html. Formal publication is expected later in the year. Changes will be incorporated into a revised *ICAP Pediatric Pocket Guide* at that time. We welcome additional suggestions for the next edition of this *Pocket Guide*, which can be sent to icap@columbia.edu. Regular clinical updates and the *Columbia Clinical Manuals* are available online at: www.columbia-icap.org/clinicalunit.

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1. List of Abbreviations

AB	Antibody	FTT	Failure to thrive
ABC	Abacavir	GI	Gastrointestinal
AFASS	Acceptable, feasible, affordable, safe, sustainable	HA	Headache
AIDS	Acquired Immunodeficiency Syndrome	HAART	Highly Active Antiretroviral Therapy
ALT	Alanine aminotransferase	Hb	Hemoglobin
ANC	Absolute neutrophil count	HC	Head circumference
ART	Antiretroviral therapy	HIV	Human immunodeficiency virus
ARV	Antiretroviral	Ht	height
AST	Aspartate aminotransferase	IDV	Indinavir
AZT	Zidovudine	IRS	Immune reconstitution syndrome
BUN	Blood urea and nitrogen	LDS	Lipodystrophy
CD4	T-lymphocyte CD4+	LGE	Linear gingival erythema
CNS	Central nervous system	LIP	Lymphocytic interstitial pneumonia
CTX	Cotrimoxazole	mo	month
d4T	Stavudine	MTCT	Mother-to-child transmission
ddI	Didanosine	NFV	Nelfinavir
DBS	Dried blood spot	NNRTI	Non-nucleoside reverse transcriptase inhibitor
DNA	Deoxyribonucleic acid	NRTI	Nucleoside reverse transcriptase inhibitor
DOT	Directly observed therapy	NVP	Nevirapine
EFV	Efavirenz	OHL	Oral hairy leucoplakia
FBC	Full blood count	OI	Opportunistic infection

PCR	Polymerase chain reaction	TB	Tuberculosis
PGL	Persistent generalized lymphadenopathy	TDF	Tenofovir disoproxil fumarate
PI	Protease inhibitor	TEN	Toxic epidermal necrolysis
PMTCT	Prevention of mother-to-child transmission (of HIV)	TLC	Total lymphocyte count
/r	Low dose ritonavir	Toxo	Toxoplasmosis
RNA	Ribonucleic acid	TST	Tuberculin skin test
RT	Randomized Trial	URTI	Upper respiratory tract infection
RTI	Reverse Transcriptase Inhibitor	WBC	White blood cell count
RTV-PI	Ritonavir boosted PI	WHO	World Health Organization
SJS	Steven Johnson Syndrome	Wt	weight
SQV	Saquinavir	yr	year



2. Diagnosing HIV in Infants and Children

Routine antibody testing, including rapid tests, should be used to diagnose HIV infection in children ≥ 18 months of age (Figure 2a). Accurate diagnosis of HIV infection in infants is more complex and requires special laboratory testing. Virologic tests, primarily DNA and RNA PCR should be used in infants (Figure 2b). For children < 18 months of age in settings where virologic testing is not available, WHO has developed criteria for presumptive diagnosis of severe HIV disease for the purpose of enabling initiation of treatment in very ill children in whom the diagnosis cannot be confirmed (Table 2 and Figure 2c). Confirmation of the presumptive diagnosis of HIV infection should be sought as soon as possible.

Breastfeeding poses ongoing risk for HIV transmission and diagnostic testing should be done at 6-12 weeks after complete cessation of breastfeeding.



Table 2: WHO clinical criteria for presumptive diagnosis of severe HIV disease in infants and children < 18 months of age

In situations where virologic testing is **not** available, a presumptive diagnosis of severe HIV disease should be made if:

- Infant is confirmed antibody positive; *and*
- Diagnosis of any Clinical Stage 4 or AIDS-indicator condition(s) can be made; *or*
- 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; *or*
- CD4 < 20% in the infant

Confirmation of the presumptive diagnosis of HIV infection should be sought as soon as feasible with the best national or locally available test for age but at the latest with HIV antibody testing at 18 months of age.

* As per IMCI definition:

- Oral thrush: Creamy white to yellow soft small plaques on red or normally colored mucosa which cannot easily be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender and not responding to topical antifungal treatment.
- Severe pneumonia: Cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs; lethargic or unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.
- Severe sepsis: Fever or low body temperature in a young infant with any severe sign such as fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, etc.

**Figure 2a: ICAP algorithm for antibody testing in children
≥ 18 months of age**

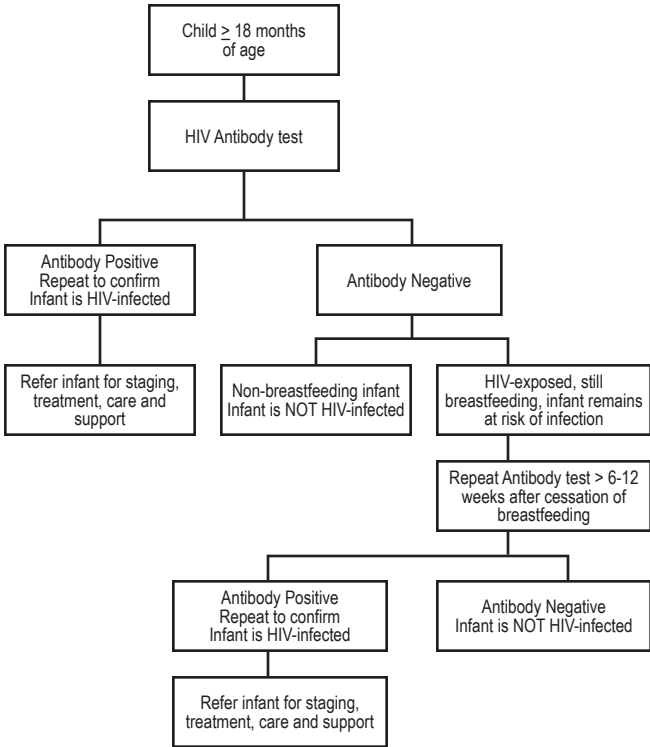
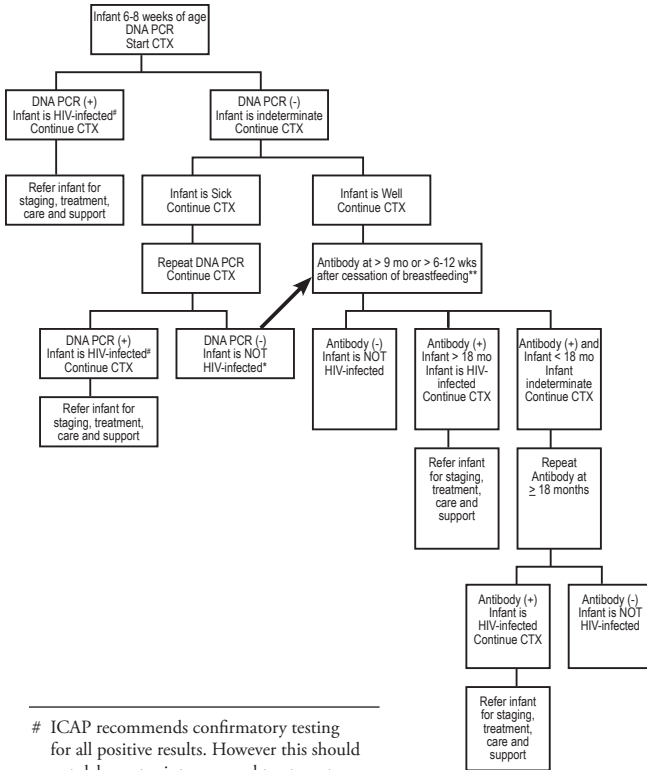


Figure 2b: ICAP diagnostic algorithm for HIV-exposed infants < 18 months of age

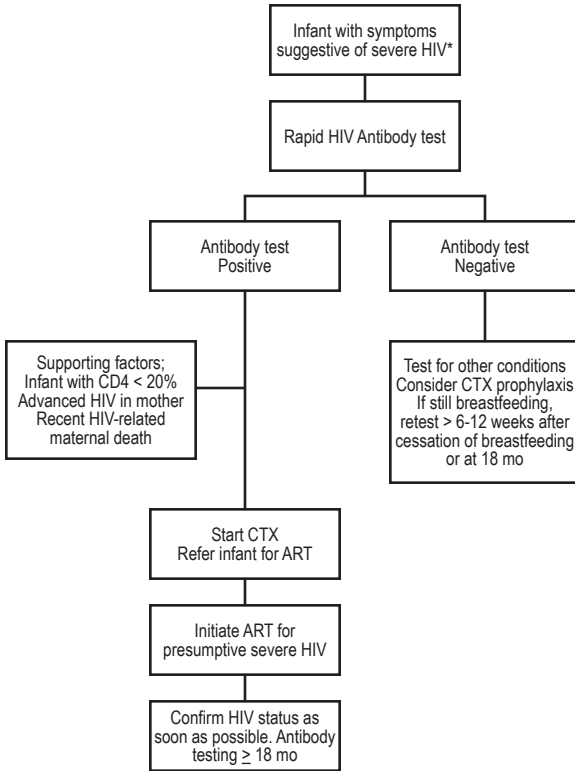


ICAP recommends confirmatory testing for all positive results. However this should not delay entry into care and treatment. Refer infant for staging and treatment whilst waiting for confirmatory test results.

* Infants with two negative (-) DNA PCR who are no longer breastfeeding are unlikely to be HIV-infected. If infant is still breastfeeding, antibody test should be performed > 6-12 weeks after cessation of breastfeeding.

** Whichever comes later.

Figure 2c: WHO diagnostic algorithm for HIV-exposed infants < 18 months in settings where virologic testing is not yet available



* Infant < 18 months of age with Clinical Stage 4 or AIDS defining condition(s) or symptomatic with two or more of the following: oral thrush, severe pneumonia or severe sepsis

3. Care of the HIV-Exposed Infant

The care of the HIV-exposed infant centers around three basic goals:

- Identify the infected child
- Prevent opportunistic infections
- Maximize family health and well-being

At each visit, review the following:

- History (birth, interim history, and parental concerns)
- Growth and nutrition evaluation (Section 11)
- Developmental assessment – developmental checklist (Table 3a)
- Physical exam – symptom/sign checklist (Table 3b)
- OI prophylaxis (Section 5)
 - ♦ CTX for PCP prophylaxis starting at 4-6 weeks until HIV is excluded (Table 5a)
- Determination & evaluation of infection status (Figure 2b and 2c)
- Assessment and plan

Follow-up schedule for HIV-exposed infants:

- Monthly until 6 months, then every 3 months until 18 months of age.
- Infants who are determined not to be HIV-infected can be discharged and followed up per local and national guidelines.

Table 3a: ICAP developmental checklist

Age	Milestones
1 month	Raises head and chest when prone, responds to sound, vocalizes, follows moving object to midline
2 months	Holds head up, lifts chest off table, smiles socially, recognizes primary care giver, hands together, makes sounds — eh, ugh
3 months	Supports on forearms in prone, holds head up steadily, hands open at rest, recognizes most familiar adults, coos
4 months	Rolls back to front, reaches for objects, laughs, orients to voice, puts objects or toys in mouth
5 months	Rolls over from stomach to back, imitates speech sounds, e.g. makes razzing sounds, reacts differently to strangers
6 months	Sits unsupported, transfers objects from one hand to the other, babbles, reaches for familiar persons
9 months	Pulls to stand, uses finger and thumb to pick up small objects, waves bye-bye, says "mama"
12 months	Walks alone, imitates actions, uses two words together
15 months	Walks backward independently, imitates action, feeds self with spoon
18 months	Runs, kicks a ball, can remove garment of clothing, scribbles, uses 6 words
2 years	Walks up and down stairs, can wash hands, combine words, follows two step command
3 years	Catches a ball and balance on one foot, can put on shirt, speech is understandable
4 years	Can dress alone, draws a person, use complex speech

Table 3b: ICAP symptom/sign checklist

Symptom / Sign			
<input type="checkbox"/> Cough	<input type="checkbox"/> Headache	<input type="checkbox"/> Thrush	<input type="checkbox"/> OHL
<input type="checkbox"/> Nausea	<input type="checkbox"/> Difficulty breathing	<input type="checkbox"/> Lymphadenopathy	<input type="checkbox"/> LGE
<input type="checkbox"/> Diarrhea	<input type="checkbox"/> Night sweats	<input type="checkbox"/> Rash	<input type="checkbox"/> Parotitis
<input type="checkbox"/> Vomiting	<input type="checkbox"/> Memory problems	<input type="checkbox"/> Hepatomegaly	<input type="checkbox"/> Weight loss/ FTT
<input type="checkbox"/> Fever	<input type="checkbox"/> Depression	<input type="checkbox"/> Splenomegaly	<input type="checkbox"/> Visual problems
<input type="checkbox"/> Poor appetite	<input type="checkbox"/> Fatigue	<input type="checkbox"/> Weakness	<input type="checkbox"/> Abdominal pain



4. Care of the HIV-Infected Child

The goals of care for the infected child are to:

- Promote health and well-being
- Prevent disease progression

At each visit, review the following:

- History (past, interim, parental concerns)
- Growth and nutrition evaluation (Section 11)
- Developmental assessment – developmental checklist (Table 3a)
- Physical exam – symptom/sign checklist (Table 3b)
- Laboratory evaluation (Table 6c)
- Clinical staging (Table 4a)
- Immunological staging (Table 4b)
- OI prophylaxis (Section 5)
 - ♦ CTX prophylaxis (Tables 5a)
 - ♦ TB screening (Table 5b)
- ARV Eligibility (Tables 4c and 4d)
- Assessment & Plan

Follow-up for HIV-infected infants and children:

- 0-6 mo: monthly
- 6-24 mo: every 3 months
- > 24 mo: if symptomatic every 3 months, if asymptomatic every 6 months
- Follow-up of children on ART (Table 6c)



Table 4a: WHO clinical staging for infants and children < 15 years of age
<p>Primary HIV Infection</p> <ul style="list-style-type: none"> • Asymptomatic • Acute Retroviral Syndrome
<p>Clinical Stage 1/ Asymptomatic</p> <ul style="list-style-type: none"> • Asymptomatic • PGL
<p>Clinical Stage 2/ Mild</p> <ul style="list-style-type: none"> • Unexplained persistent hepatosplenomegaly, papular pruritic eruptions • Extensive wart virus infection • Extensive molluscum contagiosum, recurrent oral ulcerations • Unexplained persistent parotid enlargement • Linear gingival erythema • Herpes Zoster, fungal nail infection • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, tonsillitis)
<p>Clinical Stage 3/ Advanced</p> <ul style="list-style-type: none"> • Moderate unexplained malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhea (14 days or more) • Unexplained persistent fever (above 37.5°C, intermittent or constant for longer than one month) • Persistent oral candidiasis (outside neonatal period), oral hairy leucoplakia • Acute necrotizing ulcerative gingivitis/periodontitis • Pulmonary or lymph node TB • Severe recurrent bacterial pneumonia • Unexplained anemia (< 8g/dl), and/or neutropenia (< 500/mm³) and or thrombocytopenia, (< 50,000/mm³) for > 1 month • Chronic HIV-associated lung disease including bronchiectasis • Symptomatic Lymphoid Interstitial Pneumonitis • HIV-associated cardiomyopathy or HIV-associated nephropathy
(continued next page)

Table 4a: WHO clinical staging for infants and children < 15 years of age (continued)**Clinical Stage 4/ Severe**

- Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy
- *Pneumocystis carinii* pneumonia
- Recurrent severe bacterial infections (empyema, pyomyositis, bone or joint infection, and meningitis excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous > 1 month, visceral of any duration), Kaposi's sarcoma, extrapulmonary TB
- Esophageal candidiasis (or candida of the trachea, bronchi or lungs)
- CNS toxoplasmosis (outside the neonatal period), HIV encephalopathy
- CMV infection (retinitis or CMV infection affecting another organ, with onset at age over 1 month), extrapulmonary cryptococcosis including meningitis
- Disseminated endemic mycosis (e.g. extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis), chronic cryptosporidiosis, chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Acquired HIV-associated rectal fistula, Cerebral or B-cell Lymphoma
- Progressive multifocal leucoencephalopathy (PML)

Table 4b: WHO classification of HIV-associated immunodeficiency in infants and children

Classification of HIV-associated immunodeficiency	Age –related CD4 values			
	< 11 months (%)	12-35 months (%)	36-59 months (%)	> 5 years (cells/mm ³)
Not significant	> 35	> 30	> 25	> 500
Mild	30-35	25-30	20-25	350-499
Advanced	25-30	20-25	15-20	200-349
Severe	< 25	< 20	< 15	< 200 or < 15%

Table 4c: WHO criteria for severe immunodeficiency in infants and children				
Immunological marker^a	Age specific recommendation to initiate ART^b			
	< 11 mo	12-35 mo	36-59 mo	≥ 5 yrs
CD4 % ^c	< 25%	< 20%	< 15%	< 15%
CD4 cells/mm ³	1500	< 750	< 350	< 200
To be used only in the absence of CD4 assays for children with clinical stage 2 disease				
	< 11 mo	12-35 mo	36-59 mo	5-8 yrs
TLC cells/mm ³	< 4000	< 3000	< 2500	< 2000
<p>a. Immunologic markers supplement clinical staging.</p> <p>b. ART should be initiated by these CD4 cutoff levels, regardless of clinical stage. A drop of CD4/TLC below these levels significantly increases risk of mortality.</p> <p>c. CD4% is suggested for children <5 years.</p>				

Table 4d: Summary of WHO antiretroviral eligibility criteria		
Clinical Stage	Immunologic marker	Recommendation
Stage 4*	CD4	Treat all
	No CD4	Treat all
Stage 3*	CD4	Treat all Except children > 1 year with TB** OHL, LIP, thrombocytopenia where ART initiation may be deferred if CD4 is above threshold to initiate ART
	No CD4	Treat all
Stage 2	CD4	Treat if CD4 is:
		< 25% or < 1500 cells/mm ³ for infant < 11 months
		< 20% or < 750 cells/mm ³ for child 12-35 months
		< 15% or < 350 cells/mm ³ for child 36-59 months
	No CD4	TREAT IF TLC IS:
		< 4000 cells/mm ³ for infant ≤ 11 months
< 3000 cells/mm ³ for child 12-35 months		
< 2500 cells/mm ³ for child 36-59 months		
Stage 1	CD4	Treat if CD4 is:
		< 25% or < 1500 cells/mm ³ for infant < 11 months
		< 20% or < 750 cells/mm ³ for child 12-35 months
		< 15% or < 350 cells/mm ³ for child 36-59 months
	No CD4	< 15% or < 200 cells/mm ³ for child ≥ 5 years
		Do not treat
<p>* Stabilize any OI before initiating ART</p> <p>** Pulmonary TB: Evaluate possibility to defer initiation of ART depending on assessment of clinical status and CD4, and clinical and immunological response to TB therapy (see TB section).</p>		

5. OI Prophylaxis

CTX prophylaxis for PCP prevention:

- All HIV-exposed infants should be placed on CTX until HIV status is determined. All HIV infected children < 12 months should receive PCP prophylaxis. For infants and children > 12 months with HIV, PCP prophylaxis is determined by clinical stage and CD4 count where available (Table 5a).

TST for TB screening:

- ICAP supports the use of routine TST in HIV-infected children for the purposes of identifying and treating children with latent TB infection (Table 5b).

Table 5a: ICAP guidelines for starting CTX prophylaxis in HIV-exposed and infected infants and children

- All HIV-exposed infants starting at 4-6 weeks until no longer breastfeeding and HIV has been excluded
- All infants with a presumptive clinical diagnosis of severe symptomatic HIV until no longer breastfeeding and HIV has been excluded
- All HIV-infected children < 12 months of age
- All HIV-infected children with:
 - ◆ Clinical symptoms suggestive of HIV/AIDS*
 - ◆ Prior PCP infection
 - ◆ Evidence of immune dysfunction including:
 - CD4 % less than 15%
 - In children 1-5 years CD4 < 500
 - In children > 6 years CD4 < 200

* WHO clinical stage 3 or 4 disease

Table 5b: ICAP TST for TB screening	
All HIV-infected children should have annual TST starting at 12 months of age or at the time of diagnosis for older children.	
If TST is positive (> 5mm)	Exclude active TB per local and national guidelines.
	Provide INH (10-15mg/kg, maximum 300mg) daily for 9 months (with pyridoxine per local guidelines).
Other indications	INH should also be given to all children under the age of 3 years who are in contact with an adult diagnosed with active TB disease.
	INH prophylaxis should also be considered for any child with known contact with an active case of TB.
	INH should not be given to children who have previously received INH prophylaxis, were previously treated for TB, have contraindications to INH, or who are suspected to have active tuberculosis.

6. Antiretroviral Therapy

The decision to start ART in infants and children is much more complex than in adults. It depends on the age of the child, the clinical stage and immunological assessment. Where CD4 is not available, WHO recommends using clinical staging; TLC may be used to supplement clinical staging (Tables 4c and 4d). It is important to assess patient readiness, consider drug-drug and drug-food interactions, coexistent conditions, as well as availability of ARVs. A diagnosis of severe HIV-related disease always requires ART irrespective of whether it is defined clinically or immunologically (Tables 2 and 4c). Criteria to determine ART eligibility for children older than 5 years of age are the same as for the adult. Tables 6a and 6b address the WHO recommended preferred first-line regimens for infants and children and how to monitor children on ART. Tables 6c and 6d detail contraindications to starting ARVs in infants and children and special instructions for administering pediatric antiretrovirals. Dosing for children is calculated based on weight or body surface area. As children grow, their medications must be adjusted accordingly. WHO is developing a dosing guide for use in resource-limited settings. For dosage of individual formulations refer to national guidelines or www.columbia-icap.org/clinicalunit for revised weight-band charts.



Table 6a: WHO recommended first-line ARV regimens for infants and children	
Dual NRTI plus NNRTI	
NRTI – AZT^a or ABC or d4T and 3TC	NNRTI – NVP^b or EFV^c
Children < 3 years of age or < 10kg	Children > 3 years of age
AZT+3TC+NVP d4T+3TC+NVP ABC+3TC+NVP	AZT+3TC+NVP/EFV d4T+3TC+NVP/EFV ABC+3TC+NVP/EFV
Other dual NRTI possible combinations AZT+ABC or d4T+ABC	
WHO recommended alternative ARV regimens for infants and children in special circumstances to simplify toxicity, co-morbidity and drug-drug interactions	
Triple NRTI^d	
AZT+3TC+ABC or d4T+3TC+ABC	
<p>a. AZT should not be given in combination with d4T.</p> <p>b. NVP should be used in infants and children < 3 yrs, avoid in post pubertal adolescent females considered adults for treatment purposes with CD4 > 250 cells/mm³.</p> <p>c. EFV is preferred in children older than 3 yrs of age; it should be avoided in post pubertal adolescent females who are either in the 1st trimester of pregnancy or are sexually active and not receiving adequate contraception.</p> <p>d. Children receiving treatment for TB or pregnant adolescents with CD4 > 250 cells/mm³ where both NVP and EFV have contraindications.</p>	

Table 6b: ICAP clinical and laboratory monitoring for infants and children initiating and receiving ART		
	At baseline	During therapy
Clinical	<ul style="list-style-type: none"> • History • Symptom/sign checklist • Growth and nutritional assessment • Developmental assessment • Detailed physical exam • Staging of HIV disease • Determination of co-morbid conditions/OIs • Assessment of child and caregivers readiness for therapy and adherence counseling • Follow-up weekly for the first 8 weeks 	<ul style="list-style-type: none"> • Interim history • Symptom/sign checklist • Growth and nutritional assessment • Developmental assessment • Targeted physical exam • Staging of HIV disease • Determination of co-morbid conditions/OIs • Adherence with caregiver/child • ARV prescription, recalculate dose at each visit • Referral for support services as needed • Follow-up monthly
Laboratory	<ul style="list-style-type: none"> • CD4 percentage and/or count • Hemoglobin • WBC and differential • AST, ALT, BUN and creatinine • Other laboratory parameters as per clinical indication 	<ul style="list-style-type: none"> • CD4 percentage and/or count every 3 months for children 6-18 mo of age, then every 6 months for children > 18 mo • Hb at one month for those on AZT, then symptom directed • Screening for TB annually • Other laboratory parameters as per clinical indication

Table 6c: ICAP medical contraindications to initiation of first-line ART regimen			
Contraindication	Definition	Comments	Recommendation
Severe anemia	Hb \leq 6.9 g/dL	Contraindication to AZT use	Use alternate first-line regimen: d4T+3TC+NVP or EFV ABC+3TC+NVP or EFV
Severe neutropenia	ANC \leq 250mm ³	AZT use requires close monitoring	First-line regimen may be started, but ANC measurement should be repeated within 2 weeks of initiation. If repeat shows ANC has fallen, make a single drug substitution (Table 7c).
Severe renal insufficiency	Creatinine \geq 3 times normal	Contraindication to ARV use	Patient not currently eligible for ART. Conduct diagnostic evaluation as per local guidelines and reassess for ARV eligibility if renal function improves. Expert consultation recommended if available.
Severe hepatic insufficiency	LFTs \geq 5x normal	Contraindication to NVP use	EFV can be initiated in children > 3yr or > 10kg. For smaller children PI treatment is suggested.

Table 6d: ICAP pediatric ARV side effects and special instructions

Nucleoside reverse transcriptase inhibitors (NRTI)		
Drug	Side effects	Special instructions
Abacavir (ABC)	<p>Common: HA, GI upset and rash.</p> <p>Less common: lactic acidosis, hepatomegaly with steatosis.</p> <p>Life threatening: potentially fatal hypersensitivity reaction (fatigue, fever, N/V, sore throat, rash, joint and muscle pain, cough and dyspnea).</p>	<p>Can be given with food. Tablet can be mixed with small amount of water and taken immediately.</p> <p>Instruct patient on how to recognize and respond to potentially fatal hypersensitivity reaction. Patients should not interrupt therapy without consulting their healthcare provider.</p> <p>DO NOT rechallenge after hypersensitivity reaction.</p>
Didanosine (ddl)	<p>Common: diarrhea, abdominal pain, N/V.</p> <p>Less common: increased LFTs, lactic acidosis with hepatomegaly and steatosis, peripheral neuropathy, hyperuricemia.</p> <p>Life threatening: pancreatitis which is rare in children.</p>	<p>Food decreases absorption however this may not apply in children as the systemic exposure to ddl is similar in the presence or absence of food.</p> <p>If tablets are dispersed in water, at least 2 tablets of appropriate strength should be dissolved to ensure adequate buffer.</p> <p>Keep suspension refrigerated, shake well, stable for 30 days.</p> <p>Enteric formulation may be better tolerated.</p>
(continued next page)		

Table 6d: ICAP pediatric ARV side effects and special instructions (continued)		
Lamivudine (3TC)	Common: HA, nausea, abdominal pain. Less common: pancreatitis, neutropenia, increased LFTs.	Can be given with food. Store solution at room temperature (use within one month of opening). Tablet can be mixed with small amount of water and taken immediately. Side effects are rare.
Stavudine (d4T)	Common: HA and GI intolerance. Less common: peripheral neuropathy, lipoatrophy. Life threatening: lactic acidosis with severe hepatomegaly and steatosis.	Keep liquid refrigerated. Stable for 30 days. Capsules can be opened and mixed with small amount of food or water. DO NOT USE WITH AZT (antagonistic).
Zidovudine (AZT or ZDV)	Common: neutropenia, anemia, granulocytopenia, macrocytosis, and HA. Less common: myositis, myopathy, mitochondrial disease.	Can be given with food. Syrup is light sensitive, store in a glass jar. Capsule can be opened and contents dispersed or tablet crushed and combined with food or small amount of water. Large volume of syrup not well tolerated in older children. DO NOT USE WITH d4T (antagonistic).
(continued next page)		

Table 6d: ICAP pediatric ARV side effects and special instructions (continued)		
Non-nucleoside reverse transcriptase inhibitors (NNRTI)		
Drug	Side effects	Special instructions
Efavirenz (EFV)	Common: rash, somnolence, insomnia, abnormal dreams, confusion, hallucinations. Less common: increased LFTs.	Only for children ≥ 3 years or > 10 kg. Syrup requires higher dose than capsules. Can be given with food (avoid high fat foods). Capsule can be opened and added to food; To avoid peppery taste, mix with sweet food or jam. Best given at night time to avoid CNS effects.
Nevirapine (NVP)	Common: skin rash, HA, nausea, diarrhea. Less common: increased LFTs. Life threatening: Steven Johnson Syndrome, TEN, fatal hepatitis.	Store at room temperature. Can be given with food. Tablets can be divided and combined with small amount of water or food and immediately administered. Patients should be warned of rash. Do not escalate dose if rash occurs. For SJS and TEN, discontinue drug and do not rechallenge. Multiple drug interactions.
(continued next page)		

**Table 6d: ICAP pediatric ARV side effects and special instructions
(continued)**

Protease Inhibitors (PI)		
Drug	Side effects	Special instructions
Lopinavir /ritonavir (LPV/r)	Common: diarrhea, HA, nausea, vomiting, increase in blood lipids. Less common: pancreatitis, diabetes, hyperglycemia, hepatic toxicity, fat redistribution.	Preferable to store capsules and liquid in a refrigerator. Can be stored at room temp 25°C for 2 months. Should be taken with food. Capsules should not be opened or crushed, swallow whole. Tablets require no cold chain; can be used in children on full adult dose. Liquid has low volume but bitter taste.
Nelfinavir (NFV)	Common: diarrhea, nausea, vomiting, HA. Less common: asthenia, abdominal pain, rash, lipodystrophy.	Take with food. Store at room temperature. Crushed tablet preferred even for infants. Drug interactions less than with RTV/PI.
Saquinavir (SQV)	Common: diarrhea, abdominal pain, HA, nausea. Less common: lipodystrophy, hyperglycemia.	Not approved for use in children < 25kg. Administer 2 hours before meal to increase absorption. Sun exposure can cause photosensitive reaction.

7. Management of HIV-Associated TB Infection in Children

Management of infants and children with HIV-associated TB infection is complex because of the potential for multiple drug interactions and the limited options of pediatric drug formulations. The goals of treatment are to:

- ◆ Reduce morbidity and mortality
- ◆ Reduce toxicity

Table 7a details the WHO recommendations for treating TB in ART naive children. Table 7b outlines WHO recommendations for children who develop TB while on ART. All children with HIV-associated TB infection should be on CTX prophylaxis.



Table 7a: WHO recommendations for HIV-infected children not on ART newly diagnosed with TB

WHO clinical stage	Timing of ART following initiation of TB treatment	Recommended ARV regimen
Stage 4	Start ART soon after TB treatment (between 2-8 weeks following start of TB treatment).	<p>In children < 3 years</p> <ul style="list-style-type: none"> • Preferred: 2NRTI + Ritonavir • Alternative: Triple NRTI regimen • Alternative: 2 NRTI + NVP <p>In children ≥ 3 years</p> <ul style="list-style-type: none"> • Preferred: standard 2 NRTI + EFV • Alternative: Triple NRTI regimen
Stage 3	<p><i>Where CD4 is not available, clinical management alone:</i></p> <p>Start ART soon after TB treatment (between 2-8 weeks following start of TB treatment).</p>	<ul style="list-style-type: none"> • Regimens as recommended above. • Where ART can be deferred until after completion of TB treatment, initiation with a standard 2NRTI + 1NNRTI first line regimen is preferred.
	<p><i>Where CD4 is available:</i></p> <p>Evaluate possibility to defer initiation of ART depending on assessment of clinical status and CD4, and clinical and immunological response to TB therapy:</p> <p><u>Severe and advanced immunodeficiency^a:</u> Initiate ART soon after TB treatment (between 2-8 weeks following start of TB treatment).</p> <p><u>Mild or no immunodeficiency^a:</u> Initiation of ART may be deferred until after completion of TB therapy; closely monitor response to therapy and re-assess for ART after TB therapy. If no improvement consider starting ART.</p>	

a. Definitions for immunodeficiency as per tables 4b and 4c

Table 7b: WHO recommendations for HIV-infected children already on ART newly diagnosed with TB			
Time of TB diagnosis in relation to ART	Underlying cause of TB	Consideration for ART following initiation of TB treatment (with a rifampin-containing regimen)	ARV regimen
Child on standard first line-regimen (2NRTI + 1NNRTI) diagnosed with TB	TB due to primary infection (consider at anytime during ART, depending on exposure to TB).	Continue ART but assess for need for change in ART regimen- response to TB therapy should be used to evaluate need for change.	Preferred: continue on standard 2 NRTI + 1 NNRTI first line regimen if using EFV,
	TB as part of immune reconstitution syndrome (consider in first 3 months of ART).		Alternative: switch to 2NRTI +Ritonavir if < 3 years and on NVP if possible.
	TB as sign of treatment failure of first-line regimen (consider only after 24 weeks of ART).		Switch to second line regimen.
Child on standard second-line regimen (NRTI/ NNRTI + boosted PI) diagnosed with TB	TB due to primary infection (consider at anytime during ART, depending on exposure to TB).	Assess need for changing or stopping ART regimen-response to TB therapy should be used to evaluate need for change.	Continue same regimen, consider adding RTV to achieve full therapeutic RTV dose (increase RTV until same dose as LPV in mg).
	TB as sign of treatment failure of second-line regimen (consider only after 24 weeks of ART).		Consider consultation with experts for construction of a salvage regimen. Consider stopping ART until completion of TB therapy. Consider consultation with experts for construction of a salvage regimen.

8. ART Toxicity

General approach to toxicity in children:

1. Establish whether the event is due to the ARV or another medication. Alternative explanations for the toxicity must be excluded before it is concluded the reaction is secondary to the ARV drug.
2. Exclude other disease processes; immune reconstitution syndrome, opportunistic infections, other intercurrent illness. Toxicities that have a non-ARV etiology do not require a change of the ARV drug.
3. Determine the severity of the event (mild, moderate, severe, life-threatening).
4. Manage the adverse event according to severity (Table 8a and 8b):
 - a. Severe life-threatening: immediately discontinue all ARVs, manage the medical event, reintroduce ARV using a modified regime (substitute the offending drug) when the patient is stabilized (Table 8c).
 - b. Severe reactions: substitute offending drug without stopping ART (Table 8c).
 - c. Moderate reactions: consider continuation of ART as long as feasible, if patient does not improve may consider single drug substitution.
 - d. Mild reactions: bothersome but do not require change in therapy.
5. If there is need to discontinue ART because of life threatening toxicity, stop all ARVs at once. The NNRTIs have a long half-life and some experts recommend continuing dual NRTI backbone for 7 days after discontinuation of the NNRTI drug. However, in situations of life-threatening toxicity all drugs should be discontinued at once.

Table 8a: ICAP clinical symptoms requiring medication switch

Symptom	
Nausea	Severe discomfort or minimal intake for ≥ 3 days
Vomiting	Severe vomiting of all foods/fluids in 24 hours or orthostatic hypotension or IV therapy required
Diarrhea	Bloody diarrhea or orthostatic hypotension or IV therapy required
Fever	Unexplained fever of $> 39.6^{\circ}\text{C}$ (103°F) $> 1-2$ weeks
Headache	Severe or requires narcotics
Severe life-threatening rash	Moist desquamation, ulceration, or mucous membrane involvement, Angioedema, SJS (rash with constitutional findings: fever, oral lesions blistering facial edema, conjunctivitis), TEN, erythema multiforme, exfoliative dermatitis, or necrosis requiring surgery
Allergic reaction	Angioedema or anaphylaxis
Peripheral neuropathy	Severe discomfort, objective weakness, loss of 2-3 previously present reflexes or absence of 2-3 previously present sensory dermatomes
Fatigue	Normal activity reduced by $\geq 50\%$



Table 8b: ICAP laboratory parameters requiring medication switch	
Parameter	
Hematology	
Hemoglobin	≤ 7.0 g/dL
Absolute neutrophil count	≤ 250 mm ³
Chemistry	
Bilirubin	$\geq 3x$ upper limit of normal
Creatinine	$\geq 1.2-1.5$ (<2yr), $1.7-2.0$ (>2yr)
Liver function test	
AST/SGOT	$\geq 10x$ upper limit of normal or rapidly increasing
ALT/SGPT	$\geq 10x$ upper limit of normal or rapidly increasing
Pancreatic enzymes	
Amylase	$\geq 2-3x$ upper limit of normal
Lipase	$\geq 2-3x$ upper limit of normal
Medication changes based on laboratory values should be carefully considered. Repeat testing should be done, and consider the rate of change over time.	

Table 8c: WHO recommendations for single drug substitutions for early toxicity		
Primary regimen	Most frequent significant toxicity for the ARV drug	Suggested first-line ARV drug substitution^a
ABC	Hypersensitivity reaction	AZT
AZT	Severe anemia or neutropenia ^b	d4T or ABC
	Lactic acidosis	ABC
	Severe GI intolerance ^c	d4T or ABC
d4T	Lactic acidosis	ABC
	Peripheral neuropathy	AZT or ABC
	Pancreatitis	
	Lipoatrophy/metabolic syndrome ^d	
EFV	Persistent and severe CNS toxicity ^e	NVP
	Potential teratogenicity ^f	
NVP	Acute symptomatic hepatitis ^g	EFV ^h
	Hypersensitivity reaction	Change regimen to <ul style="list-style-type: none"> • Triple NRTI (may be less potent) • PI based (premature use of 2nd line ARV drug) • Consultation with an HIV expert is recommended
	Severe life-threatening rash, SJS ⁱ	
3TC	Acute pancreatitis (very rare)	Consultation with an HIV expert is recommended
(continued next page)		

Table 8c: WHO recommendations for single drug substitutions for early toxicity (continued)

- a. Alternative explanations for the toxicity must be excluded before it is concluded the reaction is secondary to the ARV drug. Toxicities that have a non-ARV etiology do not require a change of the ARV drug. Drug substitution should only be done for severe or life-threatening toxicity.
- b. Table 8b
- c. Severe nausea, vomiting or diarrhea that prevents ingestion of ARV regimen. Table 8a
- d. Substitution of d4T typically does not reverse lipoatrophy but may slow its progression. In children ABC or AZT can be considered as alternatives; in adults, TDF can be substituted for d4T but TDF is currently not approved for use in children.
- e. Defined as severe CNS toxicity such as persistent hallucinations or psychosis.
- f. Adolescent girls in 1st trimester pregnancy or sexually active and of childbearing potential not receiving adequate contraception.
- g. Symptomatic NVP-associated hepatotoxicity is very rare in HIV-infected children prior to adolescence.
- h. EFV cannot be given to children < 3 yr of age or < 10kg due to lack of dosing information and pediatric formulation. It should not be given to adolescent girls who are sexually active not receiving adequate contraception, are in the first trimester of pregnancy or where there is a risk of pregnancy.
- i. Table 8a. For life-threatening rash, most clinicians would not substitute EFV due to potential for NNRTI class specific toxicity. Where PI is chosen as a substitute drug, LPV/r or SQV/r (in children weighing > 25kg) can be considered; NFV can be considered as an alternative.

9. Treatment Failure

The most common reason for treatment failure is inadequate adherence. Treatment failure is defined by using clinical criteria and when possible CD4 criteria (Table 9a and 9b). Before changing a failing regimen, make sure the child has received at least 24 weeks of an ARV regimen and adherence has been assessed and found to be adequate. The WHO clinical staging system can be used as a guide to deciding when to change a failing regimen. The classification of the clinical stage on treatment is designated T1-T4; e.g. a 2-year-old who is clinical stage 2 pre-ART and gets started on ART because his CD4 is 12% will be designated T2. Treatment failure should be considered when a child on therapy develops clinical symptoms that are suggestive of a more severe clinical stage or recurrence of stage 3 or 4 events. Immunologic criteria for defining treatment failure should be used to supplement clinical criteria. Generally, if the child is T1 or T2 (Clinical Stage 1 or 2) at the time of treatment failure, do not change the regimen. If the child is T3 or T4 at the time of treatment failure consider changing for T3 and switch regimen for T4 (Table 9c).

Changing ARV medication should be done with caution and in case of therapeutic failure the entire regimen should be changed (Table 9d). The new second-line regimen should include 3 new drugs or at least 2 new drugs, one or more from a new class in order to increase likelihood of treatment success and minimize the risk of cross-resistance.



Table 9a: WHO criteria for clinical failure*

- Lack of or decline in growth rate in children who show an initial response to treatment (WHO clinical stage T3 or T4 – moderate or severe unexplained malnutrition not adequately responding to standard therapy despite adequate nutritional support and without explanation)
- Loss of neurodevelopmental milestones or development of HIV encephalopathy (WHO clinical stage T4)
- Occurrence of new OI or malignancies, or recurrence of infections such as oral candidiasis that is refractory to treatment or esophageal candidiasis (WHO clinical stage T3 or T4)

* Ensure that child has been on at least 24 weeks of therapy, and adherence has been assessed and considered adequate.

Table 9b: WHO criteria for immunological failure^{a, b}

- Development of age-related severe immunodeficiency after initial immune recovery*
- Development of new age-related severe immunodeficiency, in the absence of other concurrent infection explaining CD4 decrease*
- Rapid rate of decline to or below age-related threshold for severe immunodeficiency in the absence of other concurrent infection explaining the CD4 decrease*

a. Ensure that child has been on at least 24 weeks of therapy, adherence has been assessed and considered adequate.

b. At least two measurements should be available.

* Severe immunodeficiency as defined in Table 4c.

Table 9c: WHO decision making guide for switching to second-line therapy	
New or recurrent WHO clinical stage at time of treatment failure	Management strategy
Stage T1	<ol style="list-style-type: none"> 1. Do not switch to any other regimen Maintain scheduled follow-up visits Assess and offer adherence support
Stage T2	<ol style="list-style-type: none"> 1. Treat and manage new staging event Closely monitor clinical events Assess and offer adherence support Assess nutritional status and offer support Check and document CD4 Check if on treatment ≥ 24 weeks 7. Do not switch to any other regimen
Stage T3	<ol style="list-style-type: none"> 1. Treat and manage new staging event^a Closely monitor clinical response Check if on treatment ≥ 24 weeks Assess and offer adherence support Assess nutritional status and offer support Check and document CD4 Institute more frequent follow-up 8. Consider switching the regimen
Stage T4	<ol style="list-style-type: none"> 1. Treat and manage new staging event[*] Closely monitor clinical response Check if on treatment ≥ 24 weeks Assess and offer adherence support Assess nutritional status and offer support Check and document CD4 Institute more frequent follow-up 8. Switch the regimen
<p>[*] Differentiation of OI from IRS is important</p> <p>^a Pulmonary TB or lymph node (clinical stage 3) may not be an indication of treatment failure, and thus not require consideration of second-line therapy; response to TB therapy should be used to evaluate need for switching therapy.</p>	

Table 9d: WHO recommended second-line antiretroviral drug regimen			
Failure on first-line regimen	Preferred second-line regimen		
	RTI component (NRTI/NNRTI)	PLUS	PI component^a
2NRTI + 1NRTI AZT or d4T containing regimen	ddI ^b + ABC		LPV/r or SQV ^d /r or NFV ^e
ABC containing regimen	ddI ^b + AZT		
Triple NRTI	ddI ^b + EFV ^c or NVP		
<p>a. PI component listed in order of efficacy/acceptability.</p> <p>b. ddI may not need to be taken on an empty stomach in children.</p> <p>c. EFV should not be used in children < 3 yrs or < 10kg and should be avoided in post pubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not using adequate contraception.</p> <p>d. SQV/r should not be used in children < 25kg.</p> <p>e. NFV should be used instead of LPV/r or SQV/r where no cold chain is in place; it should be taken with food to improve bioavailability.</p>			

10. Adherence in Children

ARV treatment for children requires collaboration between the child and caregivers. Key to adherence are education, preparation, monitoring and ongoing support (Table 10).

Table 10: Promoting and assessing adherence	
Education	Never missing a dose, keeping to specific times, taking it the “right way”, lifelong treatment even when feeling well. Explain importance of strict adherence in simple terms with visual aids or analogies. Emphasize need for communication with healthcare team, trust, partnership and honesty.
Preparation	Address: WHO will give the medications? WHAT medications will be given and in what doses? WHEN will the medications be given? HOW will the medications be stored, measured, and administered? Preparatory tools - taste testing, training for pill swallowing, observation of dosing, role-play, behavioral reward system, anticipating problems.
Monitoring	Emphasize importance of honest reporting and importance of the multidisciplinary approach, including pharmacy. Evaluate at each visit.
Support	Provide psychosocial support (adherence buddy, support groups) and adherence aids (pillboxes, calendars, pre-pouring, labeling syringes). Do not assume once adherent always adherent.

11. Nutritional Assessment and Support

The goals of nutritional assessment and support are to:

- Use growth charts to identify malnutrition early, and children who are failing to thrive.
- Monitor HIV disease progression, and treatment efficacy for children on ART.
- Reduce MTCT through breastfeeding and reduce the risk of death from diarrhea and other childhood infections (Table 11).

Growth failure may be the first sign that an HIV-exposed infant is infected or that an infected child requires HIV therapy. All mothers who are HIV-infected should receive counseling about the risks and benefits of various infant feeding options and specific guidance in selecting the option most suitable for their situation. ICAP encourages teams to develop site-specific guidelines that are consistent with the WHO recommendations and appropriate to the local community.



Table 11: Growth and nutritional assessment for infants and children

	Recommendations
Assessing growth	<ul style="list-style-type: none"> • Weigh infant or child at every visit. Measure Ht and HC monthly for all infants, and quarterly for older children. Measure HC up until 3 yrs. • Plot Wt, Ht and HC on growth chart at each visit. <ul style="list-style-type: none"> ➢ Any child < 5th percentile or crossing percentiles should undergo prompt evaluation. ➢ Severe wasting in an HIV-infected child (< 70% of Wt/Ht for age or a reduction of 3 standard deviations from the z-score or edema of both feet) requires prompt hospital attention and consideration for ART if there is no response to standard nutritional therapy.
Nutritional assessment for infants	<ul style="list-style-type: none"> • Dietary history: verify if exclusive breastfeeding or exclusive formula feeding. Mixed feeding should be avoided. • Check adequacy of food supply and nutrition-related symptoms. • Provide multivitamins. • Provide nutritional referral and support as needed.
Nutritional assessment for older children	<ul style="list-style-type: none"> • Dietary recall, availability of food at home, nutrition-related symptoms. Children from 2 yrs to puberty should gain 2-3 kg and grow 6-8 cm per year. • Provide multivitamins. • Provide nutritional referral and support as needed.
Breast-feeding	<ul style="list-style-type: none"> • Generally, when replacement feeding is AFASS avoidance of all breastfeeding by HIV infected mothers is recommended. However since these conditions are difficult to meet for majority of mothers: EXCLUSIVE BREASTFEEDING IS RECOMMENDED DURING THE FIRST 6 MONTHS OF LIFE. • Early breastfeeding cessation is recommended for HIV-infected mothers and their infants. The age for breastfeeding cessation should take into account local circumstances, individual mother's and infant's situation and risk of replacement feeding.

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