

Initiation of Antiretroviral Treatment and Dosing in Pediatric Patients in Resource Limited Settings

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Lecture Objectives

- Identify the immunologic and clinical criteria for ARV initiation
- Understand the goals of ARV initiation
- Understand the recommended first line treatment regimens in resource limited settings
- Recognize the challenges of ARV administration in children
- Understand why dosing is particularly important in the pediatric population

Useful Terminology

- ARVs: antiretrovirals
- HAART: highly active antiretroviral therapy
- NRTI: nucleoside reverse transcriptase inhibitor
- NNRTI: non-nucleoside reverse transcriptase inhibitor
- PI: protease inhibitor

Why to Start ARVs?

- By one year of age, approximately 30% of untreated HIV-infected infants die
- By 2 years of age, 50% of untreated infants die
- Children are at risk for the regular childhood illnesses as well as opportunistic infections
- HAART improves the child's ability to respond to infections and increases survival with many living through adolescence and beyond

Goals of ARV Therapy

- To decrease HIV related morbidity and mortality
- Restore immunologic function
- Maximally and durably suppress virologic replication
- Minimize treatment toxicity
- Promote and maintain normal physical and neurocognitive growth and development
- Improve quality of life

Table 4. Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and availability of immunological markers

WHO paediatric stage	Availability of CD4 cell measurements	Age-specific treatment recommendation [A (II)]*	
		≤11 months	≥12 months
4 ^a	CD4 ^b	Treat all	
	No CD4		
3 ^a	CD4 ^b	Treat all	Treat all, CD4-guided in those children with TB, ^c LIP, OHL, thrombocytopenia
	No CD4		Treat all ^c
2	CD4 ^b	CD4-guided ^d	
	No CD4	TLC-guided ^d	
1	CD4 ^b	CD4-guided ^d	
	No CD4 ^b	Do not treat	

* Strength of recommendation/level of evidence.

a Stabilize any opportunistic infection before initiation of ART.

b Baseline CD4 is useful for monitoring ART even if it is not required to initiate ART.

c In children with pulmonary or lymph node tuberculosis the CD4 level and clinical status should be used to determine the need for and timing of initiation of ART in relation to tuberculosis treatment (see Section XII).

d Refer to Table 5 for CD4 and table 6 for TLC values.

Table 5. CD4 criteria for severe HIV immunodeficiency

Immunological marker ^a	Age-specific recommendation to initiate ART ^b [A (I)]*			
	≤11 months	12 months to 35 months	36 months to 59 months	≥5 years
%CD4+ ^c	<25%	<20%	<15%	<15%
CD4 count ^c	<1500 cells/mm ³	<750 cells/mm ³	<350 cells/mm ³	<200 cells/mm ³

* Strength of recommendation/level of evidence.

a Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging. CD4 is preferably measured after stabilization of acute presenting conditions.

b ART should be initiated by these cut-off levels, regardless of clinical stage; a drop of CD4 below these levels significantly increases the risk of disease progression and mortality.

c %CD4+ is preferred for children aged <5 years.

Table 6. TLC criteria for severe HIV immunodeficiency requiring initiation of ART; suggested for use in infants and children with clinical stage 2 and where CD4 measurement is not available

Immunological marker ^a	Age-specific recommendation to initiate ART ^b [C (II)]*			
	≤11 months	12 months to 35 months	36 months to 59 months	5 to 8 years ^c
TLC	< 4000 cells/mm ³	< 3000 cells/mm ³	< 2500 cells/mm ³	< 2000 cells/mm ³

* Strength of recommendation/level of evidence.

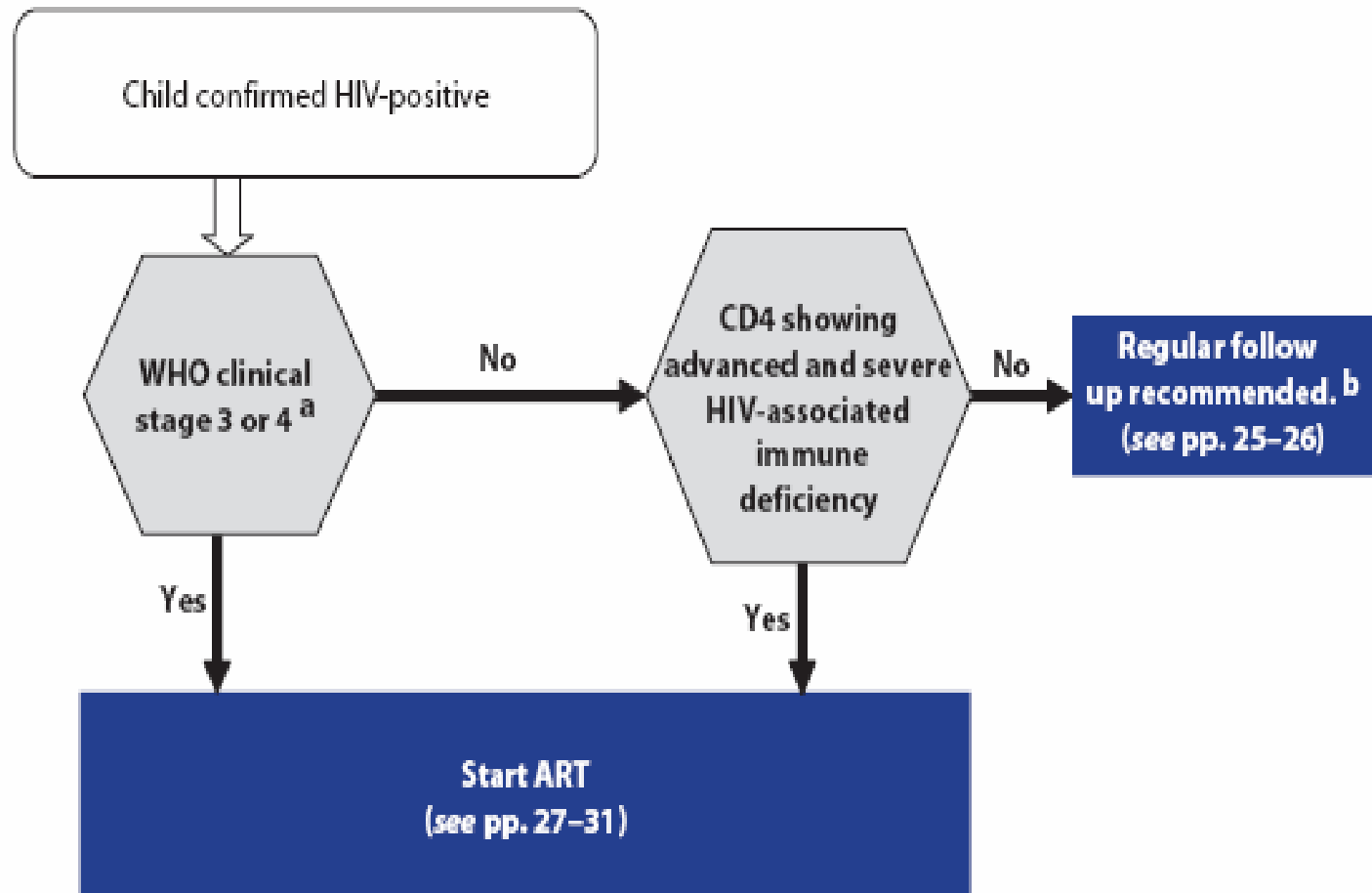
a Immunological markers supplement clinical assessment and should therefore be used in combination with the clinical staging.

b A drop of TLC below these levels significantly increases the risk of disease progression and mortality.

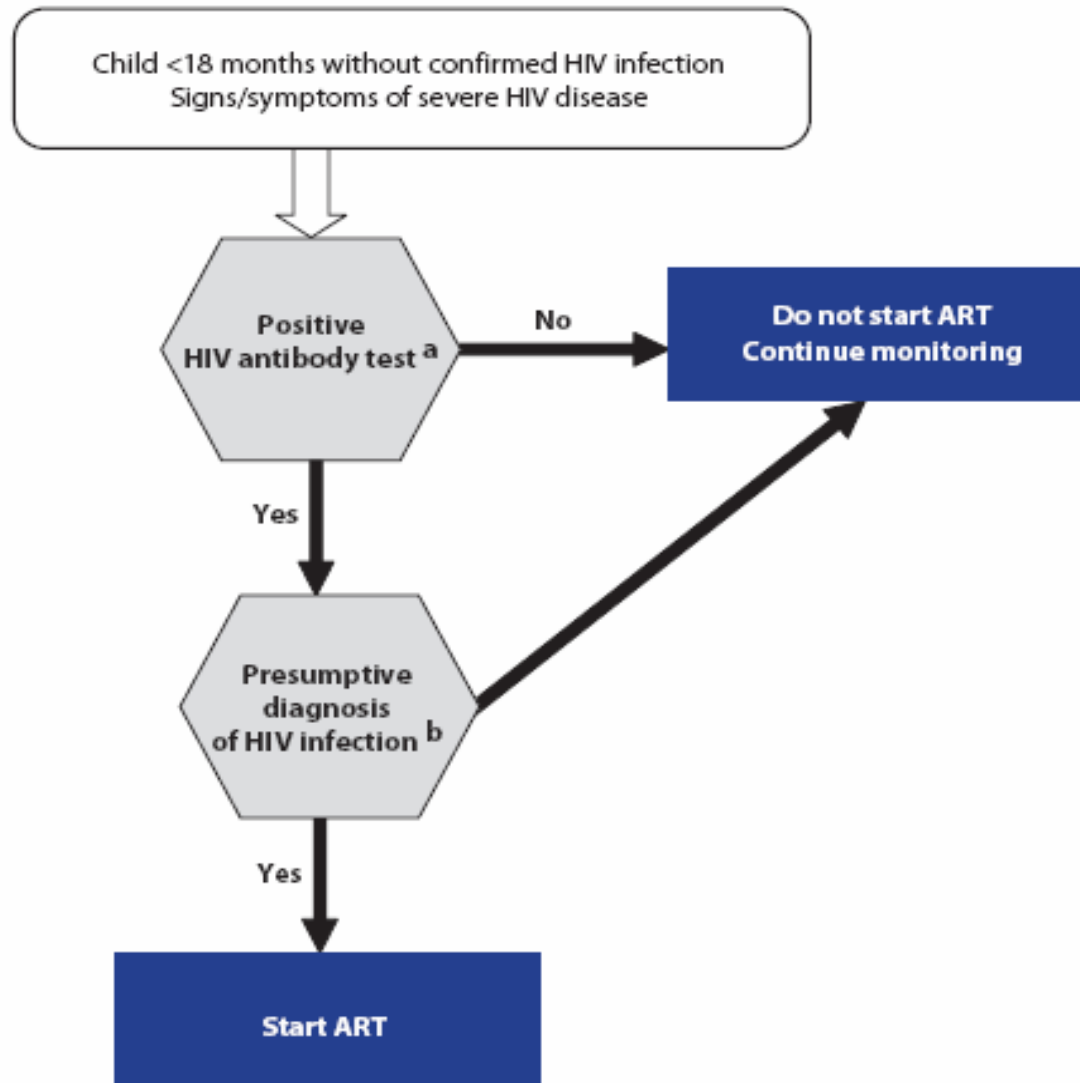
c There are fewer data available on which to base recommendations on the use of TLC for decision-making in children aged over 8 years.

An assessment of viral load (e.g. using plasma HIV-1 RNA levels) is not considered necessary before starting therapy. Because of the cost and complexity of viral load testing, WHO does not currently recommend its routine use in order to assist with decisions on when to start therapy in resource-limited settings. It is hoped, however, that increasingly affordable methods of determining viral load will become available.

8.1 Starting ART using clinical criteria



8.2 Starting ART in children less than 18 months without a confirmed diagnosis of HIV infection



Important Points about Presumptive HIV Diagnosis in Infants < 18 months old

Presumptive Dx:

1) Staging can be challenging

2) Infant has had any of the following disorders:

- PCP, Toxoplasmosis, Cryptococcal meningitis, candidal esophagitis, persistent or unexplained malnutrition

OR

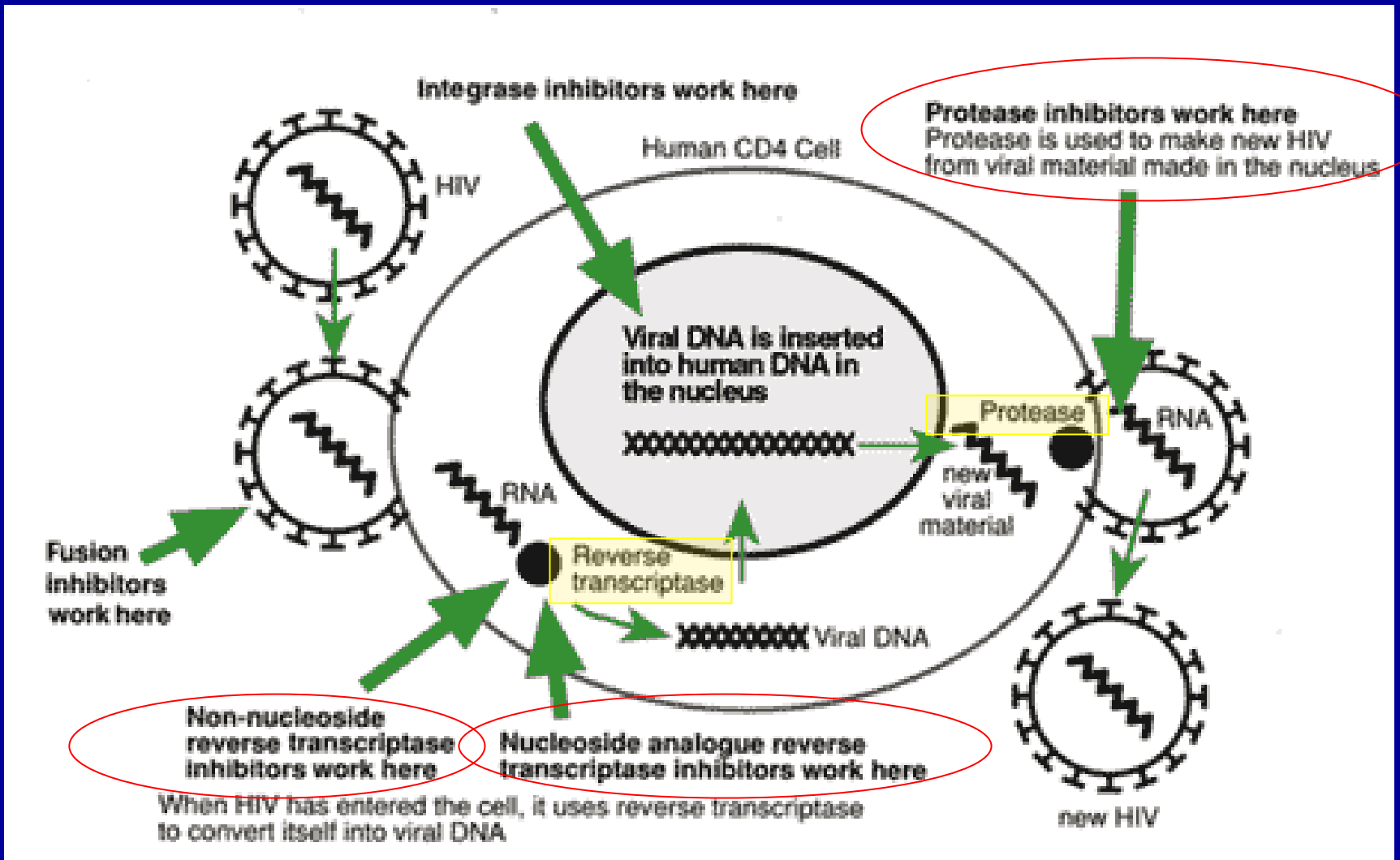
Infant is symptomatic with at least two of the following:

- Oral Thrush
- Severe pneumonia
- Severe Sepsis
- Recent HIV-related maternal death of advanced HIV disease in the mother
- CD4% < 20%

Box 2. Summary of WHO recommendations for ART initiation in infants and children

1. Infants and children with established HIV infection (as per Section IV) should be started on ART if they have:
 - WHO paediatric clinical stage 4 disease (irrespective of CD4);
 - WHO paediatric clinical stage 3 disease (irrespective of CD4, although it may add guidance); for children aged over 12 months with tuberculosis, lymphocytic interstitial pneumonia, oral hairy leukoplakia or thrombocytopaenia, ART initiation may be delayed if CD4 is available and above threshold values^a for initiating ART;
 - WHO paediatric clinical stage 2 disease *and* CD4 or TLC^b value at or below threshold;^a
 - WHO paediatric clinical stage 1 disease *and* CD4 value at or below threshold.^a
2. If virological testing is not available to confirm HIV infection, HIV antibody-positive infants and children aged under 18 months should be considered for ART if they have clinically diagnosed presumed severe HIV disease.^c

Mechanisms of Antiviral Activity



Reverse Transcriptase Inhibitors

- Block reverse transcriptase, an enzyme that facilitates the conversion of HIV RNA → DNA following virus fusion with the host cell
- There are two classes of reverse transcriptase inhibitors -nucleoside analogues (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) -based on their structure and how they inhibit reverse transcriptase.

Protease Inhibitors

- Block protease, a viral protein vital to the processing of other HIV proteins into their functional forms as they prepare to assemble into a fully active virion.
- There is only one class of protease inhibitors (PIs)

Potentially Available ARVs in Resource Limited Settings

NRTIs	NNRTIs	PIs
Zidovudine (AZT)	Efavirenz (EFV)	Lopinavir/ritonavir (LPV/r)
Lamivudine (3TC)	Nevirapine (NVP)	Indinavir (IDV)
Emtricitabine (FTC)		Saquinavir (SQV)
Abacavir (ABC)		Nelfinavir (NFV)
Didanosine (DDI)		Ritonavir* (RTV)
Tenofovir (TDF)		

*Used in combination with another protease inhibitor to enhance activity

Dosing of ARVS: Special Considerations

- Dosing by weight or by body surface area and/or Tanner staging (older children)
- Adolescent patients Tanner I and II pediatric dosing by weight
- Later Tanner stages can be dosed by adults
- Remember there may be delayed pubertal maturity in perinatally infected children
- Adolescents acquiring HIV through risk behaviors are usually older and are dosed according to adult treatment guidelines

Dosing of ARVs: Special Considerations

- Due to more rapid pharmacokinetic clearance in children, for certain ARVs (i.e. ABC, 3TC, some PIs), the pediatric dosing may actually be higher than what would be used in an adult
 - Must remember to recalculate dosing at regular intervals with height and weight gain to assure accurate dosing
- There is a lack of dosing information in children for certain ARVs (i.e. EFV in kids < 3 years of age)

Dosing of ARVS: Special Considerations

- Lack of fixed dose pediatric combinations
- Taste of liquid formulations may be unpleasant
- Cutting unscored tablets can lead to under and/or overdosing
 - It is not recommended to utilize doses requiring less than $\frac{1}{2}$ of a pill as can be unreliable
- Potential immediate and long-term toxicities of therapies

Antiretroviral Drugs & TMP/SMZ Pediatric Dosing Chart for Use in Resource-constrained Settings (see back for notes)

Weight	Abacavir (Ziagen [®])		Stavudine (Zerit [®] , d4T)	Lamivudine (EpiVir [®] , 3TC)		Zidovudine (Retrovir [®] , ZDV, AZT)		Didanosine (Videx [®] , DD)	Nevirapine (Viramune [®] , NVP)				Efavirenz (Stocrin [®] , Sustiva [®] , EFV)		Lopinavir/ritonavir (Kaletra [®])		Nelfinavir (Viracept [®])	Indinavir (Crixivan [®])	Trimethoprim/sulfamethoxazole TMP/SMZ (Septrin [®] , Bactrim [®])				
	8 mg/KG twice daily		1 mg/KG twice daily	4 mg/KG twice daily	240 mg/m ² twice daily		120 mg/m ² twice daily	Induction dose: 4 mg/KG once daily for first 14 days, then give maintenance dose →		< 8 yrs 7 mg/KG twice daily		≥ 8 yrs 4 mg/KG twice daily		Dose as shown once daily		< 15 KG = 12 mg lop/KG ≥ 15 KG = 10 mg lop/KG twice daily (lop = lopinavir, r = ritonavir)		60 mg/KG twice daily	500 mg/m ² every 8 hours	~4 mg/KG once daily (For prophylaxis against opportunistic illnesses. Doses for treatment of bacterial and protozoal infections are higher than listed here)			
KG	Liquid 20 mg/ml	Tablet 300 mg	Capsules 15, 20, 30 mg	Liquid 10 mg/ml	Tablet 150 mg	Liquid 10 mg/ml	Capsule 100 mg	Chewable tablets 25, 50, 100 mg	Liquid 10 mg/ml	Tablet 200 mg	Liquid 10 mg/ml	Tablet 200 mg	Liquid 10 mg/ml	Tablet 200 mg	Liquid 30 mg/ml	Capsules 50, 100, 200 mg	Liquid 80 mg lopinavir/r m ²	Capsule 133.3/33.3 mg lopinavir/r	Tablet 250 mg	Capsule 200 mg	Liquid 8 mg/ml	Single-strength (SS) Tablet 80mg TMP/400mg SMZ	
5 – 6.9	2 ml			2 ml		7 ml			2 ml	4 ml									2 tabs ⁷	1 cap	3 ml		
7 – 9.9	3 ml		15 mg	3 ml		9 ml	1 cap	25mg + 25mg	3 ml	6 ml						1.5 ml			2 tabs ⁷	1 cap	4 ml	½ SS tab	
10 – 11.9	4 ml		15 mg or (20 mg ¹)	4 ml		12 ml	1 cap	25mg + 25mg	4 ml	8 ml	½ tab				9 ml	200 mg	2 ml		2 tabs	1 cap	5 ml	½ SS tab	
12 – 14.9	5 ml		15 mg or (20 mg ¹)	5 ml		14 ml	1 cap	50mg + 25mg	5 ml	9 ml	½ tab				9 ml	200 mg	2 ml		3 tabs	1 cap	7 ml	1 SS tab	
15 – 16.9	6 ml		15 mg or (20 mg ¹)	6 ml	½ tab	15 ml	2 caps	50mg + 25mg	6 ml	10 ml	½ tab				10 ml	200 mg + 50 mg	2.5 ml	1 cap	3 tabs	2 caps	8 ml	1 SS tab	
17 – 19.9	7 ml	½ tab	20 mg	7 ml	½ tab	17 ml	2 caps	50mg + 50mg	7 ml	13 ml	1 tab AM + ½ tab PM ⁸				10 ml	200 mg + 50 mg	2.5 ml	2 caps ⁸	4 tabs	2 caps	9 ml	1 SS tab	
20 – 24.9	9 ml	½ tab	20 mg	9 ml	½ tab	20 ml	2 caps	50mg + 50mg	9 ml	½ tab	16 ml		9 ml	½ tab	12 ml	200 mg + 100 mg	3 ml	2 caps	5 tabs	2 caps	11 ml	1 SS tab	
25 – 29.9	25 – 27.9 KG	11 ml	½ tab	30 mg	11 ml	1 tab ³	24 ml	3 caps or 300 mg tab	100mg + 25mg	11 ml	½ tab	20 ml	1 tab	11 ml	½ tab	15 ml	200 mg + 100 mg + 50 mg	3.5 ml	2 caps	5 tabs	2 caps	14 ml	2 SS tabs
	28 – 29.9 KG	12 ml	1 tab																				
30 – 34.9	13 ml	1 tab	30 mg	13 ml	1 tab	27 ml	3 caps or 300 mg tab	100mg + 25mg	13 ml	1 tab ³		13 ml	1 tab AM + ½ tab PM ⁸	30 – 32.9 KG	15 ml	200 mg + 100 mg + 50 mg	4 ml	3 caps	5 tabs	3 caps	17 ml	2 SS tabs	
														33 – 34.9 KG	17 ml	200 mg + 200 mg							
35 – 40	15 ml	1 tab	30 mg	15 ml	1 tab	30 ml	3 caps or 300 mg tab	100mg + 25mg	15 ml	1 tab ³		15 ml	1 tab AM + ½ tab PM ⁸	17 ml	200 mg + 200 mg	5 ml	3 caps	5 tabs	3 caps	20 ml	2 SS tabs		

First Line ARV Regimens

Box 3. Summary of recommended preferred first-line ARV regimens for infants and children

Regimen of 2 NRTI plus 1 NNRTI^a

[A (II)]^{*}

AZT^b + 3TC^c + NVP^d/EFV^e

d4T^b + 3TC^c + NVP^d/EFV^e

ABC + 3TC^c + NVP^d/EFV^e

Notable Points about First Line Regimens

- NVP requires induction period of 14 days (4mg/kg/day), and if no development of rash, increasing dose to:
 - 7mg/kg BID for children <8 years old
 - 4mg/kg BID for children >8 years old
- NVP use cautioned in females with CD4 > 250 cells/mm³
- EFV not approved for children < 3 years of age and no dosing recommendations for those < 10 kg
- EFV use should be avoided in 1st trimester of pregnancy or in sexually active adolescent females not on reliable birth control
- FTC can be substituted for 3TC in children > 3 months of age

Advantages and Disadvantages of NNRTI based HAART

Advantages:

- No cold chain required (stable at room temperature)
- Relatively inexpensive
- Efficacy
- Available generic formulations
- Available fixed dose formulations

Disadvantages:

- Variable half lives
- Limitations on EFV dosing
- Low barrier to the development of resistance (NNRTIs and 3TC/FTC)

Current WHO Recommendations for Infants and Children with MTCT exposure

Box 6. Summary of recommendations on ART in infants and children exposed to ARV drugs [B (IV)]*

- Infants who were exposed to ARVs for prevention of mother-to-child transmission, either the maternal or infant component, and/or
 - Breastfeeding infants who are exposed to antiretroviral drugs because of maternal ART
- } should be considered eligible for the standard 2 NRTIs + 1 NNRTI first-line ARV regimen using the same doses and criteria as are outlined in Sections V and VI.

Research is urgently needed to identify the efficacy of ART in infants with previous or continuing exposure to ARVs.

WHO: Antiretroviral Treatment of HIV Infection in Infants and Children, 2006

Based on recent limited data, showing significant virologic failure in infants who received MTCT with NNRTIs and were subsequently treated with NNRTI-based HAART. It is possible that with further studies, these recommendations may change in the future.

Lockman et al. NEJM 2006

Box 4. Recommended alternative ARV regimen for infants and children to simplify management of toxicity, comorbidity and drug-drug interaction

Regimen of triple NRTI

[C (III)]*

AZT/d4T^a + 3TC^b + ABC

Situations where alternative ARV regimen may be considered:

- Drug intolerance
- Drug interactions (e.g. Rifamycin for anti-TB therapy)
- Adolescent females with CD4 counts > 250 and concern for initiation of NVP due to potential hepatotoxicity

Box 5. Summarizes the NRTI drug combinations that should be avoided.

Box 5. NRTI drug combinations to be avoided^a

- d4T + AZT - both drugs work through common metabolic pathways [A(I)]*
 - d4T + ddI^b - these drugs have overlapping toxicities [A(I)]*
 - TDF + 3TC + ABC^c
 - TDF + 3TC + ddI^d
 - TDF + ddI + NNRTI^e
- } these regimens are associated with a high incidence of early virologic failure [A(III)] *

Other Antiretroviral Mistakes

- Monotherapy
- Dual therapy with two NRTIs alone
- 3TC plus FTC as NRTI backbone

Expected Response to ARV

- Rapid virologic decline (1.5 to 2.0 log decline) in the first 2-4 weeks and then slower decline after (50% reaching <400 at 4 wks and approx 75% at 20 weeks)¹
- By 24 weeks virologic suppression should occur
- CD4 response may be more variable (median increase of approximately 9% in CD4% at 6 months of therapy)²

¹ Walker et al. AIDS 2004 ² Spector et al. JID 2000

Monitoring On Therapy

- Ideally the CD4 count should be repeated approximately every 2-4 months in patients on stable ART
- Viral load should be assessed every 3-4 months
- Closer monitoring intervals are recommended if: new therapy or changes in therapy, significant changes in viral load or CD4 count, or declining clinical status

Conclusions

- Initiation of therapy requires assessment of multiple factors including:
 - immunologic and clinical status
 - drug availability
 - palatability
 - dosing
 - adherence
- Virologic failure is not uncommon and will be addressed in a future lecture

References

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