Advances in Pediatric HIV

MALLIKA MOOTOO MD, POSITIVELY UNITED TO SUPPORT HUMANITY; GUYANA

Pediatric HIV Timeline

June 1983: First Reports of AIDS in children. It was concluded that MTCT can occur before, during or after birth

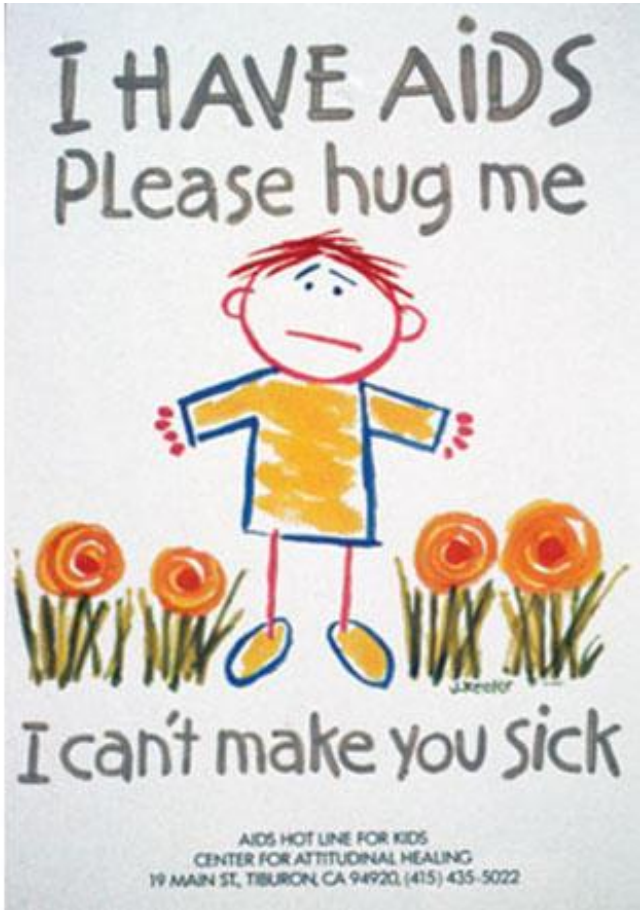
Dec.1984: Ryan White becomes infected through a blood transfusion

March 1987: AZT approved as treatment for HIV

July 1987: WHO confirms HIV can be transmitted through breast feeding

October 1990: AZT approved to treat children with HIV

1991: Didanosine approved for use in children with HIV



Pediatric ART Timeline

August 1994: AZT recommended to prevent MTCT of HIV

1995: Lamivudine approved for use with AZT

1996: Stavudine approved for children

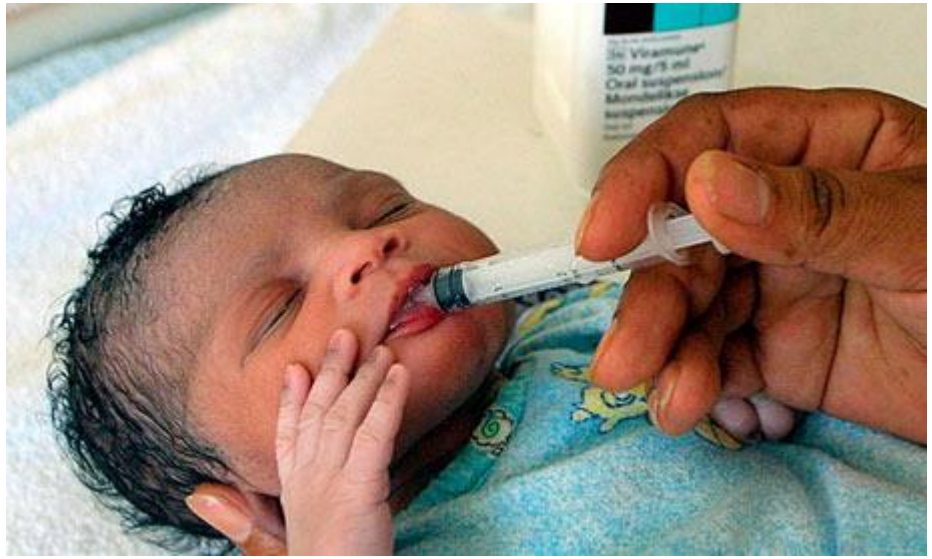
1997: Protease Inhibitors approved for use in children (Nelfinavir, Ritonavir)

1998: Nevirapine and Efavirenz (NNRTI) apoproved for children

2000: Lopinavir/ritonavir approved for children

March 2003: Fusion Inhibitors approved for children >6 years

2009: Integrase Inhibitors approved (Raltegravir)



What's New In Pediatric HIV?

BASED ON REVISIONS TO THE 2016, *GUIDELINES FOR THE USE OF ANTIRETROVIRAL AGENTS IN PEDIATRIC HIV INFECTION*

What's New?

- People First Language
- Diagnosis of HIV Infection in Infants
- Laboratory Monitoring of Pediatric HIV infection
- Which treatment regimens to use
- Adherence to ARV Therapy in Children and Adolescents Living with HIV
- Management of Children Receiving ARV Treatment
  - Modifying Regimens in Children with sustained Virologic Suppression
  - Recognizing and Managing ARV Treatment Failure

Language Edits

Incorporation of People First Language

- People First Language focuses on the person rather than the disease and recognizes the importance of language in empowering individuals and reducing stigma.

- Examples of language edits include changes from use of “HIV-infected children” to
  - “children living with HIV”
  - “children with HIV” or
  - “children with HIV infection.”

Diagnosis of HIV infection in Infants

Virologic assays that directly detect HIV must be used to diagnose HIV infection in children younger than 18 months with perinatal HIV exposure.

HIV antibody tests should not be used.

Virologic diagnostic testing is recommended at the following ages:

- 14 to 21 days
- 1 to 2 months
- 4 to 6 months

Virologic Testing at Birth

Virologic testing at birth should be considered for newborns at higher risk of perinatal HIV transmission.

E.g. infants born to mothers living with HIV who

- Did not receive prenatal care
- Did not receive antepartum nor intrapartum ARV drugs
- Received intrapartum ARV drugs only
- Were diagnosed with acute HIV infection during pregnancy
- Had detectable HIV viral load close to the time of delivery
- Received combination ARV drugs and did not have sustained viral suppression

Presumptive Exclusion of HIV Infection

HIV infection can be **presumptively** excluded in non-breastfed infants with

two or more negative virologic tests (one at age ≥14 days and one at age ≥4 weeks)

or one negative virologic test at age ≥8 weeks

or one negative HIV antibody test at age ≥6 months.

Definitive Exclusion of HIV infection

Definitive exclusion of HIV infection in a non-breastfed infant is based on two or more negative virologic tests

- one at age ≥1 month and one at age ≥4 months
- or two negative HIV antibody tests from separate specimens obtained at age ≥6 months.

Exclusion of HIV Infection

For both **presumptive** and **definitive** exclusion of HIV infection, a child must have no other laboratory or clinical evidence of HIV infection and not be breastfeeding.

Many colleagues confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at age 12 to 18 months to document seroreversion to HIV antibody-negative status.

Laboratory Monitoring of HIV Infection

Absolute CD4 T lymphocyte (CD4) cell count and plasma HIV RNA (viral load) should be measured at the time of diagnosis of HIV infection.

Should be repeated at least every 3 to 4 months until child is started on treatment .

Antiretroviral (ARV) drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy, in all treatment-naive patients.

- Genotypic resistance testing is preferred for this purpose.

What to start?

For treatment naïve patients it is strongly recommended to initiate aniretroviral treatment with 3 drugs, including either

- A boosted protease inhibitor or
- A non-nucleoside reverse transcriptase inhibitor or
- An integrase strand transfer inhibitor

Plus a dual nucleoside reverse transcriptase inhibitor backbone

Preferred Regimens

Infants, Birth to <14 Days	2 NRTIs **plus** NVP
Children Aged ≥14 Days to <3 Years	2 NRTIs **plus** LPV/r
Children Aged ≥2 Years to <3 Years	2 NRTIs **plus** LPV/r
	2 NRTIs **plus** RAL[c]
Children Aged ≥3 Years to <6 Years	2 NRTIs **plus** ATV/r
	2 NRTIs **plus** twice-daily DRV/r[d]
	2 NRTIs plus RAL[c]
Children aged ≥6 Years to <12 Years	2 NRTIs **plus** ATV/r
	2 NRTIs **plus** DTG[e]
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	2 NRTIs **plus** ATV/r
	2 NRTIs **plus** DTG[e]
	2 NRTIs **plus** once daily DRV/r[d]
	2 NRTIs **plus** EVG/COBI[f]
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to Adult and Adolescent Guidelines

Preferred Regimens

Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children, Birth to 3 Months	ZDV **plus** (3TC **or** FTC)
Children Aged ≥3 Months and <12 Years	ABC **plus** (3TC **or** FTC)
	ZDV **plus** (3TC **or** FTC)
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	ABC **plus** (3TC **or** FTC)
	TAF **plus** FTC
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to the Adult and Adolescent Guidelines

Alternative Regimens	
Children Aged >14 Days to <3 Years	2 NRTIs **plus** NVP
Children Aged ≥4 Weeks and <2 Years and Weighing ≥3 kg	2 NRTIs **plus** RAL
Children Aged ≥3 Months to <3 Years and Weighing ≥10 kg	2 NRTIs **plus** ATV/r
Children Aged ≥3 Years to <6 Years	2 NRTIs **plus** EFV
	2 NRTIs plus LPV/r
Children Aged ≥6 Years to <12 Years	2 NRTIs **plus** twice-daily DRV/r
	2 NRTIs **plus** EFV
	2 NRTIs **plus** LPV/r
	2 NRTIs **plus** RAL
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	2 NRTIs **plus** EFV
	2 NRTIs **plus** RAL
	2 NRTIs **plus** RPV

Adherence To Treatment

Adherence to antiretroviral therapy is a principal determinant of virologic suppression.

Poor adherence to ARV drugs is commonly encountered in our patients.

A variety of factors have been associated with non-adherence:

- Taste and size of medication formulation
- frequency of dosing
- drug toxicities and side effects
- child's age and developmental stage
- psychosocial and behavioral characteristics of the caregivers

Adherence Assessment and Monitoring

Strategies to maximize adherence should be discussed before initiation of ART and again before changing regimens.

Adherence to therapy must be assessed and promoted at each visit, along with continued exploration of strategies to maintain and/or improve adherence.

At least one method of measuring adherence to ART should be used in addition to monitoring viral load.

Once-daily antiretroviral regimens and regimens with low pill burden should be prescribed whenever feasible.

Routine Assessment of Medication Adherence in Clinical Care	Description
Monitor viral load.	Viral load monitoring should be done more frequently after initiating or changing medications.
Assess quantitative self-report of missed doses.	Ask patient and/or caregiver about the number of missed doses over defined period (1, 3, or 7 days).
Elicit description of medication regimen.	Ask patient and/or caregiver about the name/appearance, number, frequency of medications.
Assess barriers to medication administration.	Engage the patient and caregiver in dialogue around facilitators and challenges to adherence.
Monitor pharmacy refills.	Approaches include pharmacy-based or clinic-based assessment of on-time medication refills.
Conduct announced and unannounced pill counts.	Approaches include asking patients to bring medications to clinic, home visits, or referral to community health nursing.

Viral Load Monitoring

Most experts recommend laboratory testing at 2 to 4 weeks (and not more than 8 weeks) after initiation of ART to assess virologic response and laboratory toxicity.

Plasma viral load monitoring is important as a marker of response to ART because a fall in viral load suggests medication adherence, administration of appropriate doses, and viral drug susceptibility.

Some experts favor measuring viral load at 2 weeks to ensure that viral load is declining. A significant decrease in viral load in response to ART should be observed by 4 to 8 weeks of therapy.

Management Of Children Receiving ARV Therapy- Modifying Regimens

- Children who have sustained virologic suppression on their current regimen should be regularly evaluated for opportunities to change to a new regimen that
  - facilitates adherence
  - simplifies antiretroviral administration
  - increases ARV potency
  - decreases the risk of drug-associated toxicity.

- Past episodes of antiretroviral therapy failure, tolerability, and all prior drug resistance testing results should be considered in order to avoid choosing new ARV drugs for which archived drug resistance would limit activity.

Modifying Regimens

- Initial ARV regimens are chosen based on safety, pharmacokinetic and efficacy data for drugs available in formulations suitable for the age of the child at initiation of ART.
- New ARV options may become available as children grow and learn to swallow pills and as new drugs, drug formulations, and data become available.
- Even in the setting of sustained virologic suppression (e.g., 6–12 months) on their current regimen, changing to a new ARV regimen may be considered in order to:
  - Change from liquids to pills
  - Reduce pill burden
  - Allow use of once-daily medications
  - Reduce risk of AEs
  - Align regimens with efficacious adult regimens.
- Often the changes enhance adherence and improve quality of life.[2]

Recognizing and Managing Treatment Failure

Virologic Failure: Repeated detectable VL (>200 copies/ml) after 6 months or more of ARV therapy

Immunologic Failure: Suboptimal immunologic response to therapy or an immunologic decline while on therapy

Clinical failure is defined as the occurrence of new opportunistic infections and/or other clinical evidence of HIV disease progression during therapy.

Almost all ARV management decisions for treatment failure are based on addressing virologic failure.

Management of Virologic Treatment Failure

- Assess for adherence to therapy and medication intolerance.
- Confirm that prescribed dosing is correct for all medications in the regimen.
- The main barrier to long-term maintenance of sustained virologic suppression is incomplete adherence to medication regimens.
- Subsequent emergence of viral mutations confers partial or complete resistance to one or more of the components of the ART regimen.
- Perform ARV drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen, and before changing to a new regimen
  - Persistent viremia in the absence of detectable viral resistance to current medications is a result of nonadherence, but it is important to exclude other factors such as poor drug absorption, incorrect dosing, and drug interactions.

Management of Virologic Failure

- The new regimen should include at least 2, but preferably 3, fully active ARV medications with assessment of anticipated ARV activity based on past treatment history and resistance test results.
- The goal of therapy following treatment failure is to achieve and maintain virologic suppression.
- When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte values), prevent clinical disease progression, and prevent development of additional drug resistance that could further limit future ARV options.
- Children who require evaluation and management of treatment failure should be managed by or in collaboration with a pediatric HIV specialist.

Regimen Options After Virologic Failure with Viral Resistance

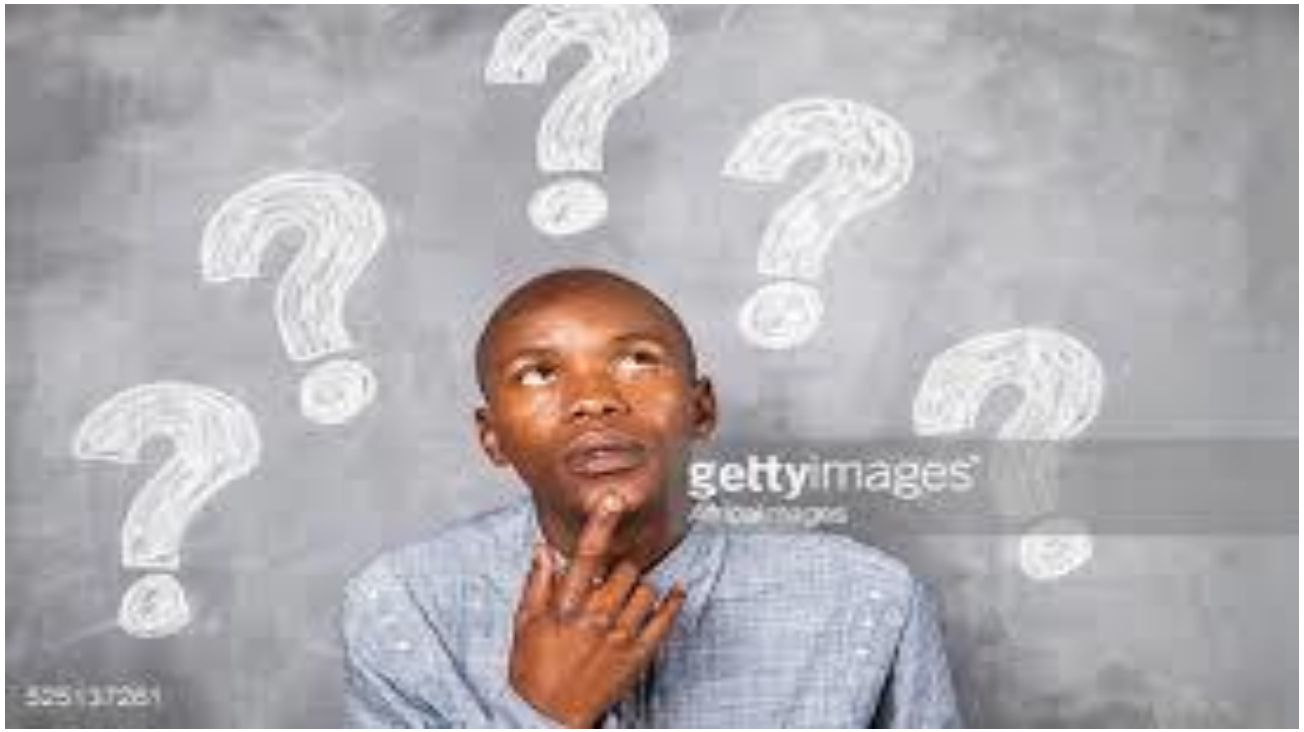
Prior Regimen	New Regimen Options
2 NRTIs plus NNRTI	•2 NRTIs plus PI •2 NRTIs plus INSTI
2 NRTIs plus PI	•2 NRTIs plus INSTI •2 NRTIs plus different RTV-boosted PI •INSTI plus different RTV-boosted PI+/- NNRTI +/- NRTI(s)
2 NRTIs plus INSTI	•2 NRTIs plus RTV-boosted PI •DTG (if not used in the prior regimen) + RTV-boosted PI +/- 1-2 NRTIs

Hurdles

Hurdles

- Our vertically infected children are living longer and getting older, many have failed both first and second line treatment options.
- There is a need for child friendly formulations including third line and salvage regimens
- Challenges of coping with disclosure of HIV status
- Coping with adolescent specific issues of education, employment, social security, sexuality, relationships, marriage and parenthood
- All these unique challenges must be recognized, understood and addressed appropriately at all levels to provide these children an opportunity in life, a chance for a better future.

Questions?



Thank you!