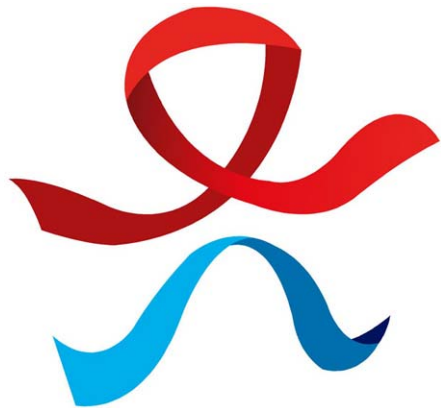


# HIV-1 Pediatric Treatment



Centro de Excelencia para Niños  
con Inmunodeficiencia

**CENID**

Hospital Nacional de Niños  
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Treatment Regional  
Technical Workshop

Santo Domingo, República Dominicana  
May 3rd, 2010

# HIV-1 Pediatric Treatment

- Pediatric ART World Situation
- When to make a diagnosis
- ~~ART~~ ART Objectives
- When to begin
- Pre-ART resistance
- What to begin with
- When to change
- Delaying the decision
- New drugs
- Summary

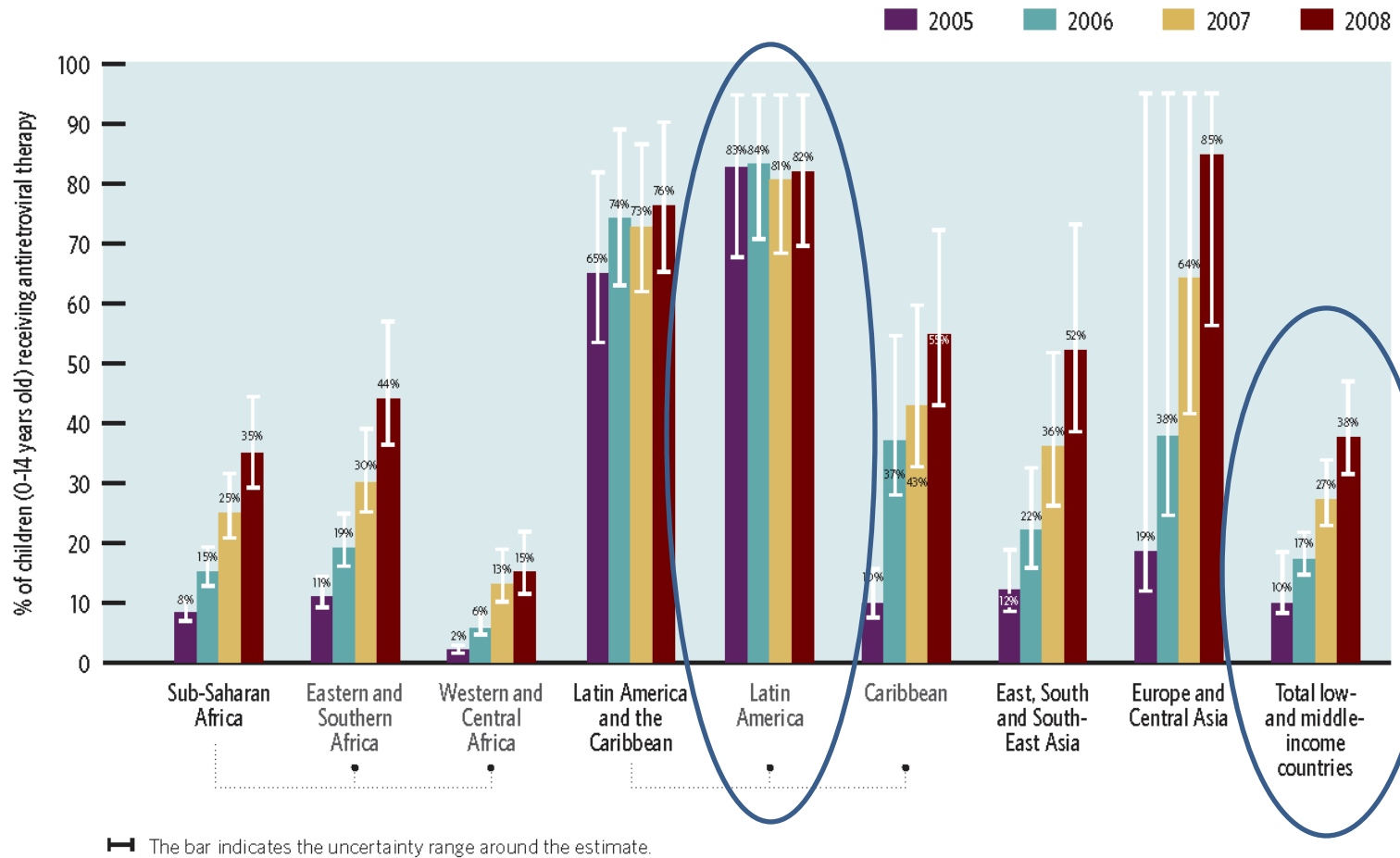
Section 1

# ° **ku WORLD 'SITUATION**

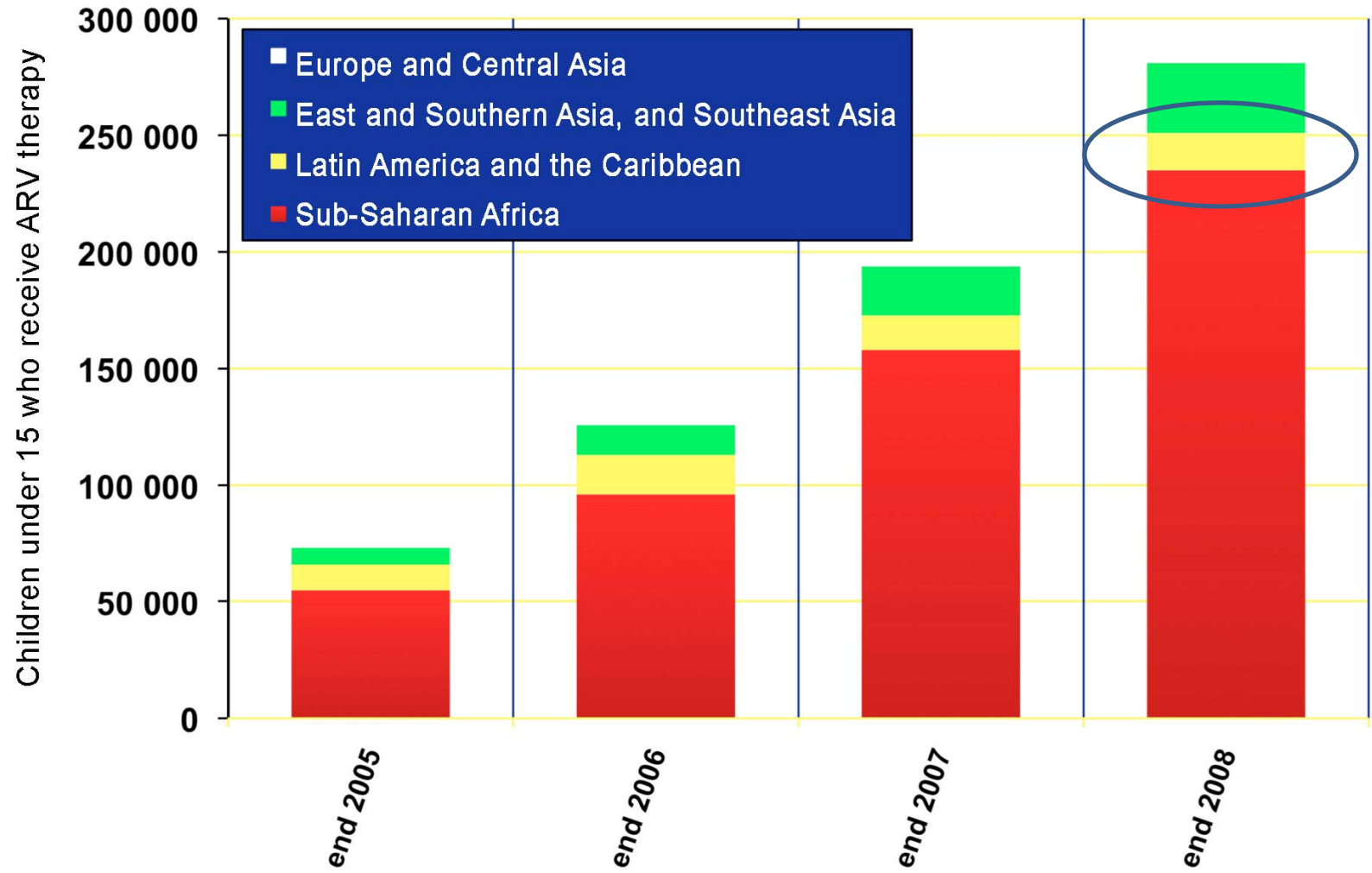
# Antiretroviral therapy coverage in low and middle income countries, children (0-14 years), December 2008

Region	Number of children reported (0-14 years) receiving ARV therapy	Estimated number of children that need therapy with ARV	Antiretroviral therapy coverage
Africa Sub-Saharan	224 900	640 000	35%
Latin America and the Caribbean	16 100	21 000	76%
East Asia, South Asia and Southeast Asia	30 000	58 000	52%
Europe and Central Asia	4 200	4 900	85%
North Africa and Middle East	400	6 700	6%
<b>Total</b>	<b>275 700</b>	<b>730 000</b> [580 000–880 000]	<b>38%</b> [31–47%]

# Percentage of children who are receiving antiretroviral therapy in low and middle income countries, 2005-2008



# Number of children (<15) who are receiving ARV in low and middle income countries, 2005-2008



# Where We Are



- **2.1 million children with HIV\***
  - ~730,000 children in need of antiretroviral treatment (ARV)
  - ~275,700 children in ART
    - Increase of 39% in 2008 coverage
    - 38% of the global need is satisfied*
    - Africa Sub-Saharan: children represent 14% of all the patients in need of ARV, but only 6% of the patients who actually receive it

\* WHO/UNAIDS/UNICEF, Towards Universal Access 2009

Section 2

# **WHEN TO MAKE A DIAGNOSIS**

# When to perform the HIV test

Population	Children exposed to HIV	Unknown exposure to HIV asymptomatic		Symptomatic
			High prevalence situations (>1% in emb )	
Recommendation	Virological Test between 4-6 weeks of life	Ask about HIV exposure	Make sure the mother/child has access to the test during the first 6 weeks of life or upon first contact with the Health Care System	Serological or virological test according to age
Recommendation Strength	Strong	Strong	Conditional	Strong

Section 3

# ° **ku OBJECTIVES**

# ART objectives for children

- Reduce the morbidity and mortality rates
- Restore and preserve the immunological system
- Enhance the quality of LIFE
- Ensure neuro-cognitive growth and development
  - Decrease the impact of HIV on the undeveloped brain
- Suppress viral replication as much as possible and for the longest time possible
  - Limited rescue options
- Minimize the toxicity induced by the drugs
  - Long term metabolic effects

# Survival data with ART

	BIPAI*	KIDS-ART-LINC**	Thailand***
Total children	5151	2142	3409
Average age (years)	5.1 – 7.8	5	7.3
Severe immunodeficiency	47-77%	65%	13%
NNRTI	90%	60%	94.7%
≥ 2nd Line	10%	5.3%	
Mortality	10% (2 years)	4.9% (12 months)	7% (12 months)

\*BIPAI: Baylor Pediatric AIDS Initiative, to August, 2006. Kline M, et al. CROI 2007, Abstract 79.

\*\*Collaboration KIDS-ART-LINC, June, 2007. Data in immunological status: Arrivé, E, et al. CROI 2007, Abstract 727

\*\*\*McConnell et al IAS 2009 Abstract MOAB101

Section 4

# **WHEN TO BEGIN**

# When to begin

- Criteria based on clinical and immunological markers in the context of the social environment
  - Benefits of preserving the immunological system surpass the toxicity and resistance risks
  - Collaborative link between the caretaker and the child
- 3 Cs 4 kids Cohort\*
  - CD4 predicts a stronger mortality
  - Malnutrition and anemia are key factors
    - weight-for-age Z scores < -3, anemia –hemoglobin <8 g/dl.
  - Total lymphocytes count is a weak predictor

\*Gibb D, et al. CROI 07, Abstract 701.

# Antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV infected infants: evidence from the Children with HIV Early Antiretroviral Therapy (CHER) Study.

*Violari A., et al.*

*4th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Abstract no. WESS103*

- Clinical Essay Phase III randomized.
- Purpose: Determine if early ART delays the progression of the disease
- Basics: Quick progression in < 1 year: Immaturity of the IS and risk of serious infections.
- Enable the development of the IS and discontinue ART until it is needed.
- Population:
  - 375 children registered < 3 months, South Africa
  - 80% ARV as PLWH (60% NVP and 20% NVP+AZT)
- Method:
  - Group 1(N:125) Beginning with ART with CD4 < 25% or clinic
  - Group 2 and 3(N:252) Beginning with ART upon diagnostic  
AZT, 3TC, LPV/r 40 and 96 weeks
- Assessed by DMSB (independent expert committee)

# Children with HIV Early Antiretroviral Therapy (CHER) Study

## Results

- Survival: 96% early ART group vs. 84% control group
- Decrease in mortality of 75%
- DMSB recommended not including children in the deferred ART group

Cause of death N: 18	° kT deferred	° kT early
Gastroenteritis	4	4
Sepsis/pneumonia	5	0
PCM/CMV	3	0
Sudden death syndrome	0	1
Liver failure	0	1
Total	12	6

# When to begin ARV for <12 months

**AIDS. 2009 Mar 13;23(5):597-604.**

## **Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants.**

[Goetghebuer T](#), [Haelterman E](#), [Le Chenadec J](#), [Dollfus C](#), [Gibb D](#), [Judd A](#), [Green H](#), [Galli L](#), [Ramos JT](#), [Giaquinto C](#), [Warszawski J](#), [Levy J](#); [European Infant Collaboration group](#).

[Collaborators \(11\)](#) [Faye A](#), [Gabiano C](#), [Thorne C](#), [Keiser O](#), [Marczynska M](#), [Ene L](#), [Hainaut M](#), [Scherpbier H](#), [Schmitz V](#), [Brichard B](#), [Verweel G](#).

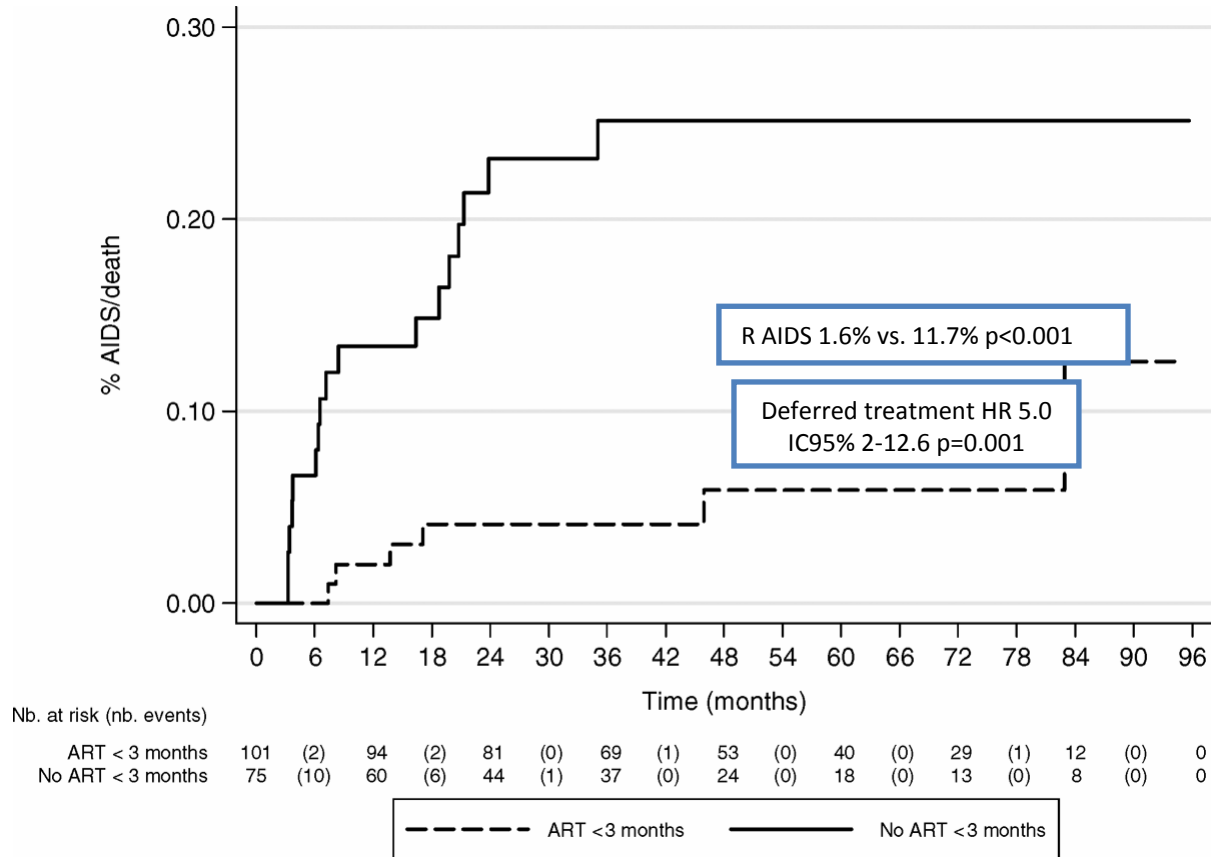
Pediatric Department, CHU St Pierre, Brussels 1000, Belgium.

**OBJECTIVE:** In the absence of treatment, rapid progression to AIDS occurs in approximately 20% of HIV-1-infected infants over the first year of life. The prognosis of these children has considerably improved with highly active antiretroviral therapy. As data from **well resourced countries** are lacking, the objective of this collaborative study was to evaluate the impact of early treatment in vertically infected infants. **DESIGN:** Children **born to HIV-infected mothers** between **1 September 1996 and 31 December 2004**, who were diagnosed with HIV and **free of AIDS before 3 months**, were eligible. Demographics and pregnancy data, details of antiretroviral therapy, and clinical outcome were collected from **11 European countries**. **METHODS:** The risk of AIDS or death, by whether or not an infant started treatment before 3 months of age, was estimated by Kaplan-Meier survival analysis and Cox proportional hazards models. **RESULTS:** Among 210 children, 21 developed AIDS and three died. Baseline characteristics of the 124 infants treated before 3 months were similar to those of the 86 infants treated later. The risk of developing AIDS/death at 1 year was 1.6 and 11.7% in the two groups, respectively (P < 0.001). Deferring treatment was associated with increased risk of progression [crude hazard ratio 5.0; 95% confidence interval (CI) 2.0-12.6; P = 0.001] that persisted after adjusting for cohort in multivariate models (adjusted hazard ratio 3.0; 95% CI 1.2-7.9; P = 0.021).

## **CONCLUSION:**

.....  
**In nursing babies infected with HIV-1 through vertical transmission of HIV-1, the beginning of ARV before 3 months is associated with a significant reduction in the progression of AIDS and death.**

# Highly effective treatment started before three months reduces the risk of progression



# When to begin

Guides	< 12 Months	1 to < 3 years	3 to 5 years	> 5 years
USA	•All	<ul style="list-style-type: none"> <li>• Significant Symptoms (CDC B or C except NIL or single episode of invasive bacterial disease)</li> <li>• CD4 &lt; 25% The symptoms don't matter</li> </ul>		<ul style="list-style-type: none"> <li>• Significant symptoms</li> <li>• CD4 &lt; 350 cel/ml</li> </ul>
PENTA	•All	<ul style="list-style-type: none"> <li>• CDC B or C</li> <li>• WHO 3 or 4</li> <li>• CD4 &lt; 25% or &lt;1000 cel/ml</li> </ul>	<ul style="list-style-type: none"> <li>• CDC B or C</li> <li>• WHO 3 or 4</li> <li>• CD4 &lt; 20% or &lt;500 cel/ml</li> </ul>	<ul style="list-style-type: none"> <li>• CDC B or C</li> <li>• WHO 3 or 4</li> <li>• CD4 &lt; 350 cel/ml</li> </ul>

Guides	CD4	< 12 Months	1 to < 3 years	3 to 5 years	> 5 years
WHO	No	All	WHO 3 and 4		
	Yes		WHO 4		
			CD4 < 750 cel/ml	CD4 < 350 cel/ml	CD4 < 200 cel/ml
			CD4% < 20%	CD4% < 20%	CD4% < 15%

# Early Treatment

## Pros

- CHILDREN < 12 months:  
Consensus based on the evidence in favor of early treatment (even though we know that 80% are not fast developers)
- OLDER CHILDREN:  
Inability to recognize complications before irreversible damage is caused.
  - Higher susceptibility to opportunistic infections and irreversible brain damage (HIV encephalopathy).
  - Count and percentage CD4 are less liable complication predictors.

## Contras

- The **adherence** is more difficult in children than in adults.
  - Many of the families living with HIV also face difficult social situations.
  - The appropriate pleasantly flavored pediatric syrup and low dosage tablets are limited and most of the syrup require refrigeration.
- Some **secondary effects** depend on the duration of the exposure to the drug ( dyslipidemias, cardiovascular risk accumulation).

# Consequences of a late start

- Increase in mortality KIDS-ART-LINC\*
  - High mortality with severe immunodeficiency at the beginning of ART
  - 6 months: 7.8% vs. 1.8%
- Less probability of immunological recovery
  - Thailand: time for CD4 >25%\*\*
    - 67% reached the goal of CD4 in an average of 72 weeks
    - CD4 base <5%: less probable of reaching the goal

\*Arrivé E, et al. CROI 07, Abstract 727.

\*\*Puthanakit T, et al. IAS 07, Abstract TUPEB131.

Section 5

# **PRE-ARU RESISTANCE**

# Pre-ART resistance

Data supporting basal genotyping

	1998-99 N=91*	2001-02 N=42**	2002-05 N=21***	1997-2004 N=60****
Any resistance	12.1%	19.1%	23.8%	20%
NRTI	7.7%	7.1%	14.3%	16%
NNRTI	3.3%	11.9%	19.0%	3%
PI	3.3%	2.4%	0%	1.6%
> 2 classes	2.2%	2.4%	9.5%	

\*Parker MM, et al. *JAIDS*2003;32:292-7.

\*\*Karchava M, et al. *JAIDS*2006;42:614-9.

\*\*\*Persaud D, et al. *J Infect Dis*2007;May15;195(10):1402–10. PACTG 1030

\*\*\*\*Delaugerre C, et al *Retrovirology*. 2009; 6: 85.

# Early resistance

## Impact on the regime sustainability

- Post-PMTCT

- Botswana: 30 <12 months in ART with NVP\*

- ~8.5 months (media)

- VF at 6 months AR T, 77% in exposed to SD NVP vs. 9% placebo

- IMPAACT P1060\*\*

- Exposed or not to SD NVP
  - <12 months and >12 months
  - ART: NVP Vs. LPV/r
  - VF at week 24
    - NVP 24%
    - LPV/r 7%

- In ART

- Argentina: 40 children in ART with NVP or NFV\*\*\*

- 90% with no perinatal exposure before ARV
  - 5.5 months (media) of ART, 70% development >1 “primary” mutation
  - Primary mutations included K103N, Y181C, G190A, V106A, M184V, M41L.

\*Lockman S, et al. *N Engl J Med* 2007;356:135-47.

\*\* Palumbo P. et al, IAS 2009, Abstract LBPEB12

\*\*\*Vignoles M, et al. IAS 2007, Abstract TUPEB054.

Section 6

# **WHAT TO START WITH**

# Available ARV

## NFH=

- ✓ Abacavir (ABC)
- ✓ Didanosine (ddl)
- ✓ Emtricitabine (FTC)
- ✓ Lamivudine (3TC)
- ✓ Stavudine (d4T)
- Tenofovir (TDF)
- ✓ Zidovudine (AZT, ZDV)

## NNFH=

- Delavirdine (DLV)
- ✓ Efavirenz (EFV)
- Etravirine (ETR)
- ✓ Nevirapine (NVP)

## P=

- ✓ Atazanavir (ATV)
- ✓ Darunavir (DRV)
- ✓ Fosamprenavir (FPV)
- Indinavir (IDV)
- ✓ Lopinavir (LPV)
- ✓ Nelfinavir (NFV)
- ✓ Ritonavir (RTV)
- Saquinavir (SQV)
- ✓ Tipranavir (TPV)

## Fusion inhibitors

- ✓ Enfuvirtide (ENF, T-20)

## CCR5 antagonists

- Maraviroc (MVC)

## Integrase inhibitors

- Raltegravir (RAL)

✓ = Approved by the FDA for use with children

# What to start with

POPULATION	< 12 MONTHS	1-4 YEARS	>5 YEARS
START OF ART	PMTCT with exposure to NVP: Regime with PI No PMTCT: Regimen with NVP	2 NRTI + NVP/EFV	2 NRTI + NVP/EFV
Recommendation Strength	Strong	Strong	Strong

# What to start with

- Standard first line, WHO 08
  - 2 NRTI: (AZT or d4T or ABC) + 3TC
  - 1 NNRTI: NVP or EFV
  - 1 PI: LPV/r\*
- AZT preferred over d4T\*\*
  - Thailand: 57% of the children in d4T had lipodystrophy at week 144\*\*\*

\*The LPV/r dosage for <6 months and < 5 kg based on a 300mg/m<sup>2</sup> dosage

\*\*WHO SEARO/UNICEF ROSA. Management of HIV Infection and ART in Infants and Children, December 2006. AZT preferred if hemoglobin >7.5 g/dl

\*\*\*Aurpibul L, et al. IAS 07, Abstract TUPEB127

# What to start with

## PENPACT 1 (PENTA 9/PACTG 390)

- N=266
- Random selection initially with NNRTI or PI
- Second randomization
- HIV RNA change  $>1,000$  or  $>30,000$  copies/ml
  - Primary “Endpoint”: Viral replication 4 years after the initial randomization.
  - The sub-study will address the prospective development of lipodystrophy and metabolic anomalies.

Section 7

# **DELAYING FAILURE**

# Adherence support

- Mobilize resources to enhance social stability
  - Recognize the impact of poverty, death, orphanhood, stigma and violence on the ability of the family to take care of their children.
- Encourage the disclosure of the diagnosis
  - When it is appropriate, both culturally and psychologically.
- Prepare for the transition to adolescence

# Use the best drugs/regimens

- NVP vs. EFV
  - Thailand (N=107): 64% (NVP) vs. 91% (EFV) virological suppression at week 72 (p=0.001)\*
    - CD4: 19.4% (NVP) vs. 22.7% (EFV), p=0.03
  - Uganda (N=250): Risk of failure with NVP at 12 months of ART (OR 3.33; CI 1.51, 7.36)\*\*
- NNRTI vs. PI
  - South Africa (N=389): 43% (NNRTI) vs. 60% (PI) suppression at 24 months (p=0.05)\*\*\*
    - CD4: 26.4% (NNRTI) vs. 24.6% (PI), p=0.33

\*Puthanakit T, et al. *Pediatr Infect Dis J*,

\*\*Kanya MR, et al. CROI 07, Abstract 732.

\*\*\*Jaspan HB, et al. CROI 07, Abstract 728.

# Anticipate resistance

- Provide laboratory monitoring to optimize future rescue regimes
  - CD4, viral load, genotype
  - Dry drop sampling
- Perform research on how to improve the prognosis of children
- Extend the availability of 2<sup>nd</sup> and 3rd line ARV

# ARV for children

Limited drugs/combination options

- Liquid suspensions
  - Costly, difficult to transport/distribute/store
- Cut adult tablets
  - Effective choice
    - Doctors Without Borders: 1187 children, survival probability in 12 months 0.87\*
    - Thailand: 107 children, 70% with undetectable CV at week 192\*\*
      - Inappropriate dosage for small children (<10kg)
      - Difficult to use

\*O'Brien DP, et al. *AIDS*2006;20:1955-60.

\*\*Puthanakit T , et al. *Pediatr Infect Dis J*, 2007 Oct; 26(10):953-6.

# CDF for pediatrics

- Just one regimen: d4T-3TC-NVP
  - High ratio between NVP and NRTI
    - Children under 12 months
      - 5mg-20mg-35mg
      - 6mg-30mg-50mg
    - Children
      - 10mg-40mg-70mg
      - 12mg-60mg-100mg
      - Grooved, dispersible tablets
- <60 USD/child/year

# CDF pharmacokinetic data

- CHAPAS 1, Zambia\*

- N=65

- Average age 6.9 years, weight for age Z-score -3.4
    - Dosage according to weight from Pedimune (Triomune) Baby or Pedimune Junior (Cipla)

- Levels of d4T y 3TC

- Comparable with adults

- Levels of NVP

- Therapeutical levels of the drug over all weight ranges higher than in adults
    - 6% with heavy sub therapeutical levels of C12h
    - There was no difference per age or weight with AUC12h

\*L'homme RF, AIDS. 2008 Mar 12;22(5):557-65

Ellis JC, Antivir Ther. 2007;12(2):253-60.

# CDF pharmacokinetic data

- CHAPAS 1 Sub
  - Staggered dosage Vs. Complete List of side effects\*
    - N=211
    - 92 weeks
      - Complete dosage: 18/100 persons/year EA  $\frac{3}{4}$
      - Staggered dosage: 16.5/100 persons/year EA  $\frac{3}{4}$
    - 90% of the children with complete dosage continued their ART without EA
    - Staggered dosage requires separate drug supply
  - Concomitant use with Rifampicine\*\*
    - PK of NVP
    - N=22
    - Average age: 1.55 years
      - 52% reached therapeutical levels of NVP
      - 41% decrease in AUC NVP with Rifampicine

\*Kabamba D et al. IAS 2009 Abstract MOPEB090.

\*\*Oudijk JM et al. IAS 2009 Abstract LBPEB10.

# What do we need?

- Wider range of drug options
- Dual and triple combination
- Dispersible tablets, grooved or triturable
- Granules/bags

**WHO: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children.**  
Report of the WHO Paediatric Antiretroviral Working Group

"Crowley S., et al. Ideal ARV formulations for children. : 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Abstract no. CDB300"

Section 8

# **WHEN TO CHANGE**

# When to change Failure criteria

- Clinical failure: New or recurrent clinical events in spite of ARV with proven adherence
- Immunological failure: Decrease of CD4 to the lower limits for the particular age (immunosuppressant)
- Virological failure: Increase in the Viral load

# Plan for a lifetime

- Sequence the regime until adulthood
  - Pediatric Spectrum of HIV Disease Study
    - 1997: 4% in >3rd regime
    - 2001: 17% in >3rd regime
    - The durability dropped from **13 to 7 months from the first to the third regimen\***
- Few rescue options
  - Less resistance → Delay in therapeutical failure

\*McConnell MS, et al. *J Acquir Immune Defic Syndr* 2005;38:488–494.

Section 9

# **NEW DRUGS**

# New drugs

- **The ART guidelines for children** are frequently prescribed for the **assessment of possible resistances** on the basis of prior medication history.
- With the purpose of choosing an effective regimen, **the pharmacist must use new drugs** before they have been sufficiently tested in pediatric or adolescent clinical trials.
- **More studies are required among pediatric populations**

# Available drugs

## **NRTI**

- ✓ Abacavir (ABC)
- ✓ Didanosine (ddI)
- ✓ Emtricitabine (FTC)
- ✓ Lamivudine (3TC)
- ✓ Stavudine (d4T)
- Tenofovir (TDF)
- ✓ Zidovudine (AZT, ZDV)

## **NNRTI**

- Delavirdine (DLV)
- ✓ Efavirenz (EFV)
- Etravirine (ETR)
- ✓ Nevirapine (NVP)

## **PI**

- ✓ Atazanavir (ATV)
- ✓ Darunavir (DRV)
- ✓ Fosamprenavir (FPV)
- Indinavir (IDV)
- ✓ Lopinavir (LPV)
- ✓ Nelfinavir (NFV)
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- Saquinavir (SQV)
- ✓ Tipranavir (TPV)

## **Fusion inhibitors**

- ✓ Enfuvirtide (ENF, T-20)

## **CCR5 antagonists**

- Maraviroc (MVC)

## **Integrase inhibitors**

- Raltegravir (RAL)

✓ = Approved by the FDA for use with children

# Pediatric ART

## new drugs

## Tenofovir (TDF)

Pediatr Infect Dis J. 2009 Mar;28(3):204-9.

**Tenofovir use in human immunodeficiency virus-1-infected children in the United Kingdom and Ireland.**

[Riordan A](#), [Judd A](#), [Boyd K](#), [Cliff D](#), [Doerholt K](#), [Lyll H](#), [Menson E](#), [Butler K](#), [Gibb D](#); Collaborative HIV Paediatric Study. Collaborators (18) [Boyd KL](#), [Butler K](#), [Doerholt K](#), [Donaghy S](#), [Dunn DT](#), [Gibb DM](#), [Judd A](#), [Lyll EG](#), [Masters J](#), [Menson E](#), [Murphy B](#), [Novelli V](#), [Peckham CS](#), [Riordan A](#), [Sharland M](#), [Shingadia D](#), [Tookey PA](#), [Tudor-Williams G](#).

Royal Liverpool Children's NHS Trust, Liverpool, England. [Andrew.riordan@rlc.nhs.uk](mailto:Andrew.riordan@rlc.nhs.uk)

### CONCLUSIONS:

- **TDF seems to be an effective antiretroviral drug in the pediatric cohort, even though a considerable overdosing and infradosing is possible. A small number of children experienced serious side effects while taking TDF; half had renal toxicity, mostly associated with the concomitant use of ddl and lopinavir-ritonavir.**

# Studies with PI in young people and children (IMPAACT)

- P1020A - Atazanavir and Atazanavir /r
- P1051 - Tipranavir/r
- P1058 - Raltegravir
- P394 - Tenofovir+emtricitabine
- P1049 - Darunavir
- P1071 - Vicriviroc
- P1075 - Maraviroc

# Pediatric ART

## New strategies

- **What can we do?**

- Strategies for the Management of Antiretroviral Therapy (**SMART**) study: the structured discontinuances in the treatment significantly increased the risk of OP and death by any cause in a comparison with TC.
- **PENTA 11** study (Paediatric European Network for Treatment of AIDS)
  - Once the child begins treatment it will probably be for life.
  - The only way to minimize the exposure is, therefore, to avoid beginning the treatment too soon.

# Pediatric ART

## New strategies

- Use the drugs once/day: ABC- 3TC: PENTA 15
- Scheduled discontinuance: PENTA 11
- Short cycle discontinuance: PENTA 16 (5 days on/ 2 off)
- Monotherapy with Lopinavir/r: PENTA 18

# PENPACT1-PACTG 390

Randomized study of:

- antiretroviral combination guidelines, and
- strategies to change therapy in children beginning therapy >30 days of age and < 18 years of age.

✓ Study began in the year 2000.

✓ The primary care physician chooses the initial therapy and the initial long term effect from HAART with PI vs. NA

# Summary

- Documented benefits of ARV treatment for children.
- Only 38% of the children who require ART receive it.
- More and better pediatric ARV formulations are required.
- The early diagnosis of HIV in children is critical.
- Early treatment for nursing infants can prevent the progression of the disease.

# Summary

- The delay of therapeutical failure involves a combination of social support and clinical interventions.
- More research studies are required in order to provide **good treatment alternatives** for children with previous experience.
- **The access to healthcare and psycho-social support is critical to consolidate all these benefits.**