

Keeping up with the kids

Pediatric Treatment Issues

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Sydney - IAS 2007



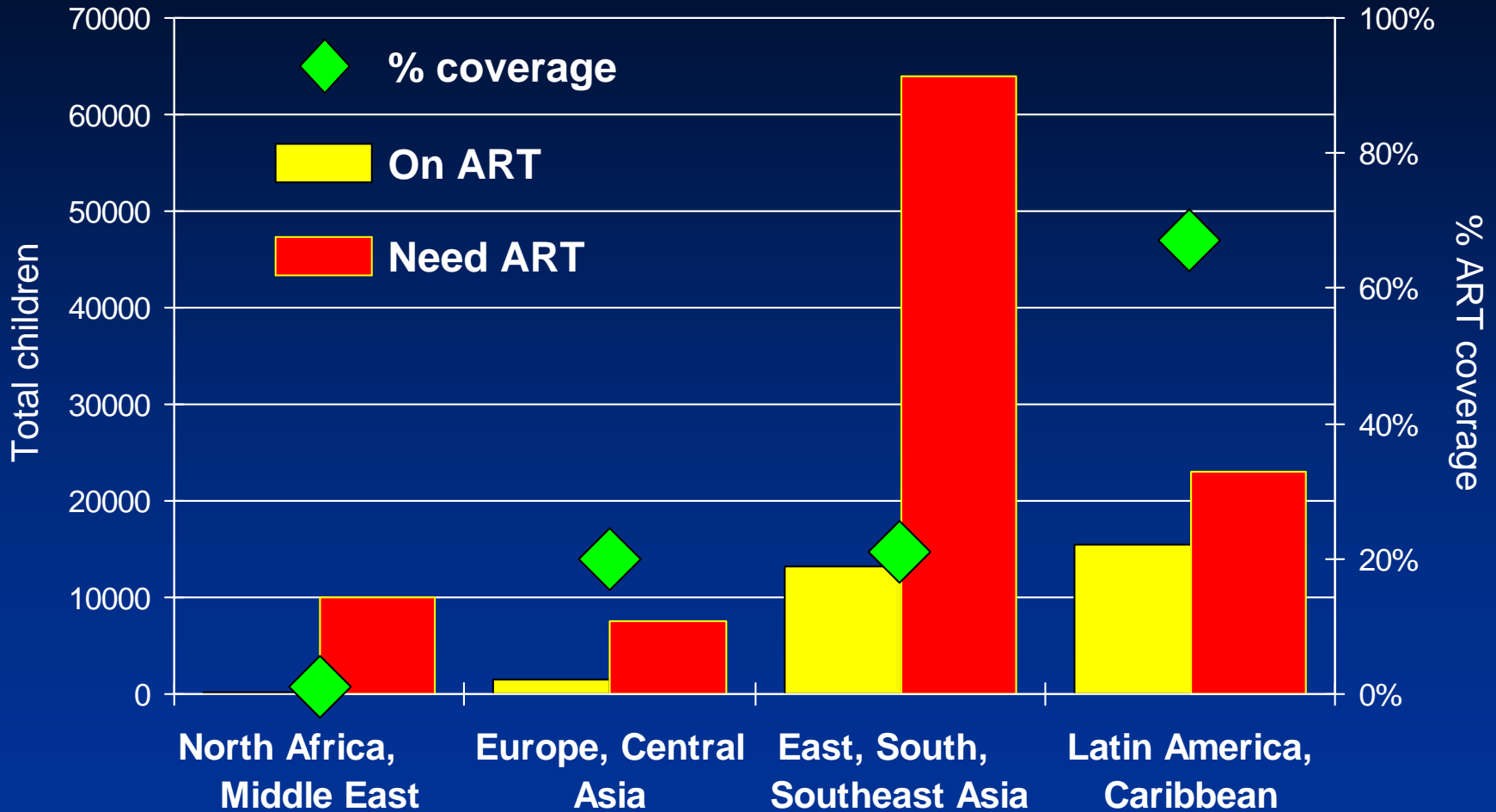
Where we are now

- **2.3 million children with HIV***
 - ~780,000 children in need of antiretroviral (ARV) treatment (ART)
 - ~115,500 children on ART
 - 50% increase in coverage in 2006
 - *15% of global need being met*
 - Sub-Saharan Africa: children represent 14% of those who need ART, but only 6% of those who receive it

*WHO/UNAIDS/UNICEF, Towards Universal Access, April 2007.

Pediatric ART

Low- and Middle-income Countries, December 06

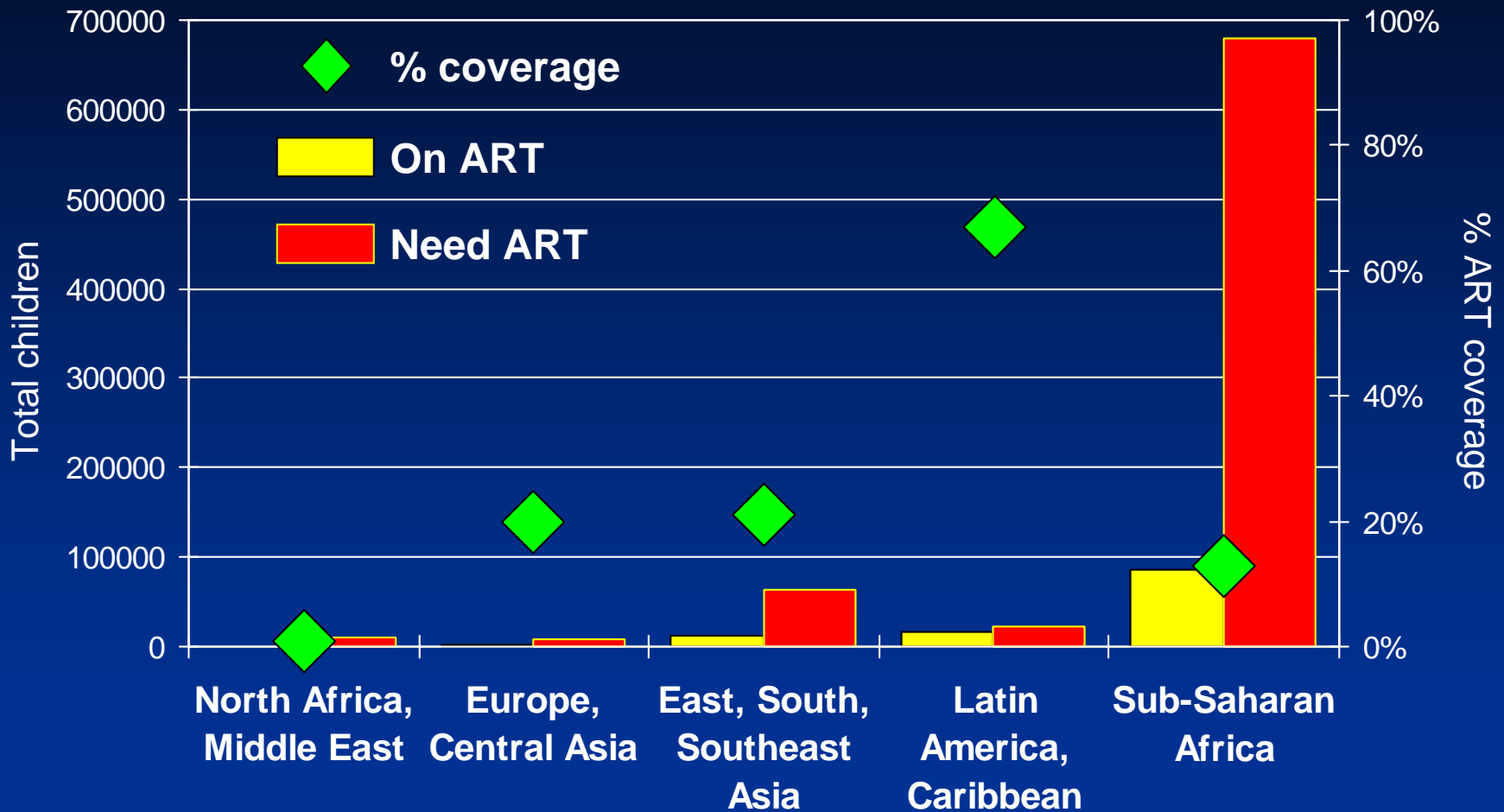


WHO/UNAIDS/UNICEF, Towards Universal Access, April 2007.

UNICEF/WHO/UNAIDS, Children and AIDS: A stocktaking report, 2007.

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Regional Surveillance Data

	BIPAI	KIDS-ART-LINC	MSF	S/SE Asia group
Total children	4062	2456	3754	12,864
Median age, years	5.1-7.8	5.0	5.7	--
Severe immune deficiency	47-77%	65%	75%	--
NNRTI regimen	90%	60%	99%	97%
≥2 nd line	10%	5.3%	0.5%	--

BIPAI: Baylor Pediatric AIDS Initiative, to August 06. Kline M, et al. CROI 07, Abstract 79.

KIDS-ART-LINC Collaboration, to June 07. Data on immune status from Arrivé, E, et al. CROI 07, Abstract 727.

MSF: Médecins Sans Frontières, to May 06. Olson D, et al. IAS 06, Abstracts MOAB0204 and MOAB0203. Data on immune status for children <5 years old with CD4 <15%.

South/Southeast Asia, national data. **Cambodia** to March 07. **India** to April 07. **Thailand** to May 07. **Vietnam** to April 07.

Goals of ART in Children

- Reduce morbidity and mortality
- Restore and preserve immune function
- Improve quality of life
- Support physical growth and neurocognitive development
 - Lessen impact of HIV on an immature brain
- Maximally and durably suppress viral replication
 - Limited salvage options
- Minimize drug-related toxicity
 - Long-term metabolic effects

When to Start

- Criteria based on clinical and laboratory markers in the context of the social environment
 - Benefits of immune preservation outweigh risks of toxicity and resistance
 - Collaborative relationship with caretakers and child
- 3Cs4kids Cohort Collaboration*
 - CD4 strongest predictor of mortality
 - Malnutrition and anemia key factors
 - Total lymphocyte count weak predictor

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

Malnutrition - weight-for-age Z scores < -3, anemia - hemoglobin <8 g/dl.

Immune Criteria

2006 WHO CD4 Thresholds

- Age-related levels for severe immune deficiency that correspond to 12-month mortality risk of $\leq 5\%$ in children >1 year of age*
 - ≤ 11 months: $<25\%$
 - 12-35 months: $<20\%$
 - 36-59 months: $<15\%$
 - >5 years old: $<15\%$ or <200 cells/mm³

*Dunn D. *Lancet* 2003;362:1605-11.

Consequences of Starting Later

- Increased mortality
 - KIDS-ART-LINC*
 - Higher mortality if severe immune deficiency at start
 - 6 months: 7.8% vs. 1.8%
- Less likely to achieve immune recovery
 - Thailand: time to CD4 >25%**
 - 67% reached target CD4
 - Median 72 weeks
 - Baseline CD4 \leq 5% least likely to reach target

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

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

Early vs. Deferred Treatment?

- Children with HIV Early ART (CHER - South Africa)*
 - Infants with CD4 $\geq 25\%$ randomized to early treatment until 1 or 2 years of age, or deferral until CD4 $< 20\%$
 - Interim analysis: 75% reduction in mortality in early treatment group
 - DSMB closed deferral arm
- PREDICT (Cambodia, Thailand)
 - Randomized trial of children with moderate immune failure
 - Immediate (CD4 15-24%) vs. deferred ($< 15\%$)

*Violari A, et al. IAS 07, Late-breaker abstract WESS103.

What to Start With

- Standard first-line, WHO 06
 - 2 NRTI: AZT or d4T or ABC *and* 3TC
 - 1 NNRTI: NVP or EFV
- AZT preferred to d4T*
 - Thailand: 57% of children on d4T regimen had lipodystrophy by 144 weeks**

*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.

ARVs for Children

Limited Range of Drugs/combinations

- Liquid suspensions
 - Expensive, harder to ship/distribute/store
- Split adult tablets
 - Effective alternative
 - Médecins Sans Frontières: 1187 children, probability of survival at 12 months 0.87*
 - Thailand: 107 children, 70% with undetectable viral load at 192 weeks**
 - Inappropriate doses for small children (<10kg)
 - More difficult to use

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

**Puthanakit T, et al. *Pediatr Infect Dis J*, in press.

ARV	Form	Company	FDA	WHO
AZT	10 mg/ml	Aurobindo	X	X
	10 mg/ml	Cipla		X
	10 mg/ml	Combino		X
	100 mg	Aurobindo	X	X
	100 mg	Cipla	X	X
	100 mg	Combino		X
d4T	1 mg/ml	Aurobindo	X	X
	15 mg	Aurobindo	X	X
	20 mg	Aurobindo	X	X
	20 mg	Aspen		X
3TC	10 mg/ml	Aurobindo	X	X
	10 mg/ml	Cipla	X	X
ABC	20 mg/ml	Aurobindo	X	X
NVP	10 mg/ml	Aurobindo	X	X
EFV	50 mg	Aurobindo	X	X
	100 mg	Aurobindo	X	X
	200 mg	Aurobindo	X	X
	200 mg	Ranbaxy		X

Approved First-line Generics, June 07

- **US FDA “tentative approval”***
 - PEPFAR-eligible
 - Of 51 first-line options, 13 at pediatric dosing range
- **WHO prequalification***
 - Of 85 first-line options, 18 at pediatric dosing range
- ***No pediatric fixed-dose combinations***

*<http://www.fda.gov/oia/pepfar.htm>

**<http://mednet3.who.int/prequal/>

Pediatric FDCs

Four Products Under WHO Review

- One regimen: d4T-3TC-NVP
 - Higher NVP to NRTI ratios
 - Infants
 - 5mg-20mg-35mg
 - 6mg-30mg-50mg
 - Children
 - 10mg-40mg-70mg
 - 12mg-60mg-100mg
 - Scored, dispersible tablets
- <60 USD/child/year



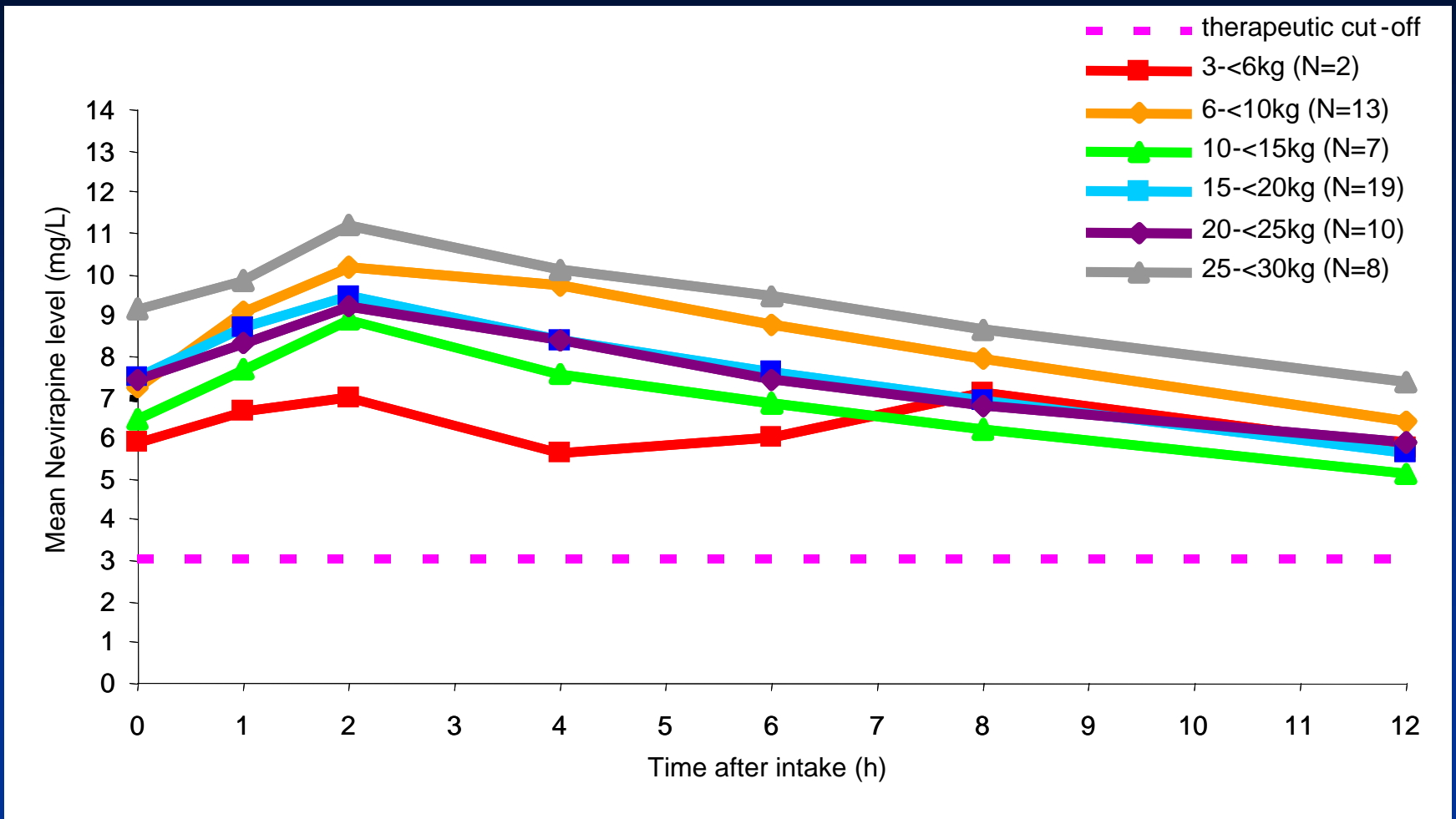
Triviro LNS Kid
Courtesy of Ranbaxy

FDC Pharmacokinetic Data

- CHAPAS 1, Zambia*
 - N=64
 - Median age 6.9 years, weight-for-age Z-score -3.4
 - Weight-based doses of Pedimune Baby or Pedimune Junior (Cipla)
 - d4T and 3TC levels
 - Comparable to adults
 - NVP levels
 - Therapeutic drug levels across all weight ranges
 - 7% with subtherapeutic trough levels at C_{\min}
 - No difference by age or weight in AUC_{12h}

*Kabamba D, et al. CROI 07, Abstract 580.

Therapeutic NVP Levels Using Pedimune FDCs, CHAPAS 1



Slide courtesy of Drs. Rafaëlla L'homme and Desiré Kabamba

What we Need

More Pediatric ARV Formulations

- Wider range of drugs
- Dual- and triple-combinations
- Scored, crushable, dispersible tablets
- Granules/sachets

Pre-ART Resistance

Data in Support of Baseline Genotyping

Type of resistance	98-99 ¹ N=91	01-02 ² N=42	02-05 ³ N=21
<i>Any resistance</i>	12.1%	19.1%	23.8%
NRTI	7.7%	7.1%	14.3%
NNRTI	3.3%	11.9%	19.0%
PI	3.3%	2.4%	0%
<u>≥2 classes</u>	2.2%	2.4%	9.5%

New York State: ¹Parker MM, et al. *JAIDS* 2003;32:292-7.

²Karchava M, et al. *JAIDS* 2006;42:614-9.

PACTG 1030: ³Persaud D, et al. *J Infect Dis* 2007;195:1402-10.

Early Resistance

Impact on Regimen Durability

- Post-PMTCT

- Botswana: 30 infants on ART with NVP*

- ~8.5 months of age (median)
- By 6 months on ART, 77% virologic failure in those exposed to single-dose NVP vs. 9% if placebo

- On ART

- Argentina: 40 children on ART with NVP or NFV**

- 90% without perinatal ARV exposure
- By 5.5 months (median) on ART, 70% developed ≥ 1 “primary” mutation

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

**Vignoles M, et al. IAS 07, Abstract TUPEB054.

Primary mutations included K103N, Y181C, G190A, V106A, M184V, M41L.

When to Switch

Treatment Failure Criteria

- New or recurrent clinical events
- CD4 falling to age-related thresholds
- Viral load rises...
 - PENPACT 1 (PENTA 9/PACTG 390)
 - Initial randomization to NNRTI or PI
 - Second randomization - switch at HIV RNA >1,000 or >30,000 copies/ml

Planning for a Lifetime

- Sequencing regimens into adulthood
 - Data to support informed decision-making
 - Pediatric Spectrum of HIV Disease Study
 - 1997: 4% on their $\geq 3^{\text{rd}}$ regimen
 - 2001: 17% on their $\geq 3^{\text{rd}}$ regimen
 - Durability fell from **13 to 7 months** from the first to the third triple-drug regimen*
- Few switch options
 - Limit resistance → delay treatment failure

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

Delaying Treatment Failure

- Support adherence
- Use the best drugs and regimens
- Anticipate resistance

Support Adherence

- Mobilize resources to improve social stability
 - Recognize the impact that poverty, death, orphanhood, stigma, and violence have on a family's ability to care for their children
- Encourage disclosure
 - When culturally- and developmentally-appropriate
- Prepare for transition to adolescence

Use the Best Drugs and Regimens

- NVP vs. EFV
 - Thailand (N=107): 64% (NVP) vs. 91% (EFV) virologic suppression at 72 weeks (p=0.001)¹
 - CD4: 19.4% (NVP) vs 22.7% (EFV), p=0.03
 - Uganda (N=250): NVP regimen predicted failure at 12 months (OR 3.33; CI 1.51, 7.36)²
- NNRTI vs. PI
 - South Africa (N=389): 43% (NNRTI) vs. 60% (PI) suppression at 24 months (p=0.05)³
 - CD4: 26.4% (NNRTI) vs. 24.6% (PI), p=0.33

¹Puthanakit T, et al. *Pediatr Infect Dis J*, in press.

²Kanya MR, et al. CROI 07, Abstract 732.

³Jaspan HB, et al. CROI 07, Abstract 728.

Anticipate Resistance

- Provide laboratory monitoring to optimize future salvage regimens
 - CD4, viral load, genotype
 - Dried blood spot testing
- Conduct research to learn how to obtain better outcomes in children
- Broaden 2nd- and 3rd-line ARV availability

Summary

- 15% of children who need ART receive it
- More and better pediatric ARV formulations are essential to expanding treatment coverage
- Data on optimal timing to initiate ART and switch regimens are increasing
- Delaying treatment failure involves a combination of social support and clinical interventions

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