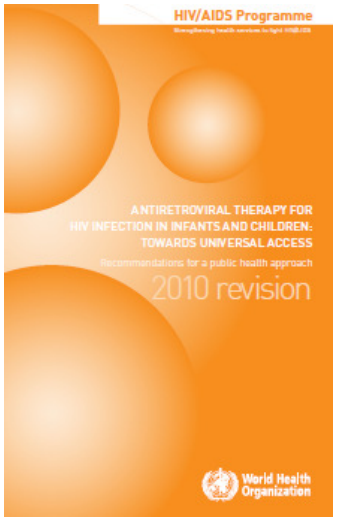
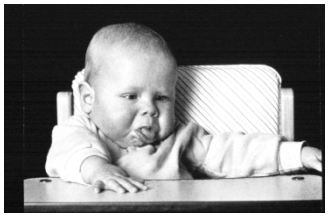
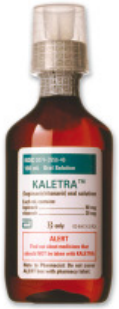
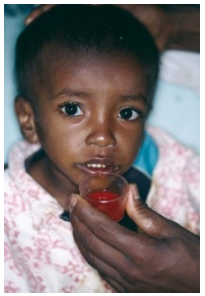
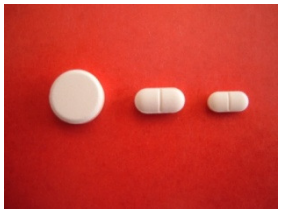






80 mg/20 mg/mL Kaletra
oral solution
[lopinavir/ritonavir]





Update on Pediatric Antiretroviral Therapy

Lynne M. Mofenson, M.D.
Pediatric, Adolescent and Maternal AIDS Branch
National Institute of Child Health and Human Development
National Institutes of Health
Department of Health and Human Services

HIV-Infected Children are Not Little HIV-infected Adults

- Age-related differences in risk of HIV disease progression and surrogate markers such as CD4
- Dosing is complex - needs adjustment as child grows to avoid under-dosing and resistance
- Differential maturation of organs leads to age-related pharmacokinetics changes and age-specific dosing
- More limited drug formulary because pediatric drug formulations are needed
- Concern regarding ARV toxicities in growing child (e.g., TDF and bone in pre-pubertal child)

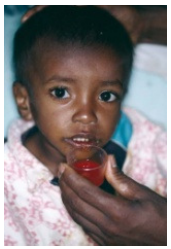
HIV-Infected Children Are Not a Uniform Group:
Age-Related Differences

- Infants and children - <2 years

  - High viral load
  - Rapid progression and high mortality with no good surrogate markers
  - PMTCT ARV drug exposure and resistance – may affects ART response
  - Fewest options – liquid/dispersible needed
  - Major changes organ development/ metabolism - affect dosing

HIV-Infected Children Are Not a Uniform Group:
Age-Related Differences

- Age 2 -5 years



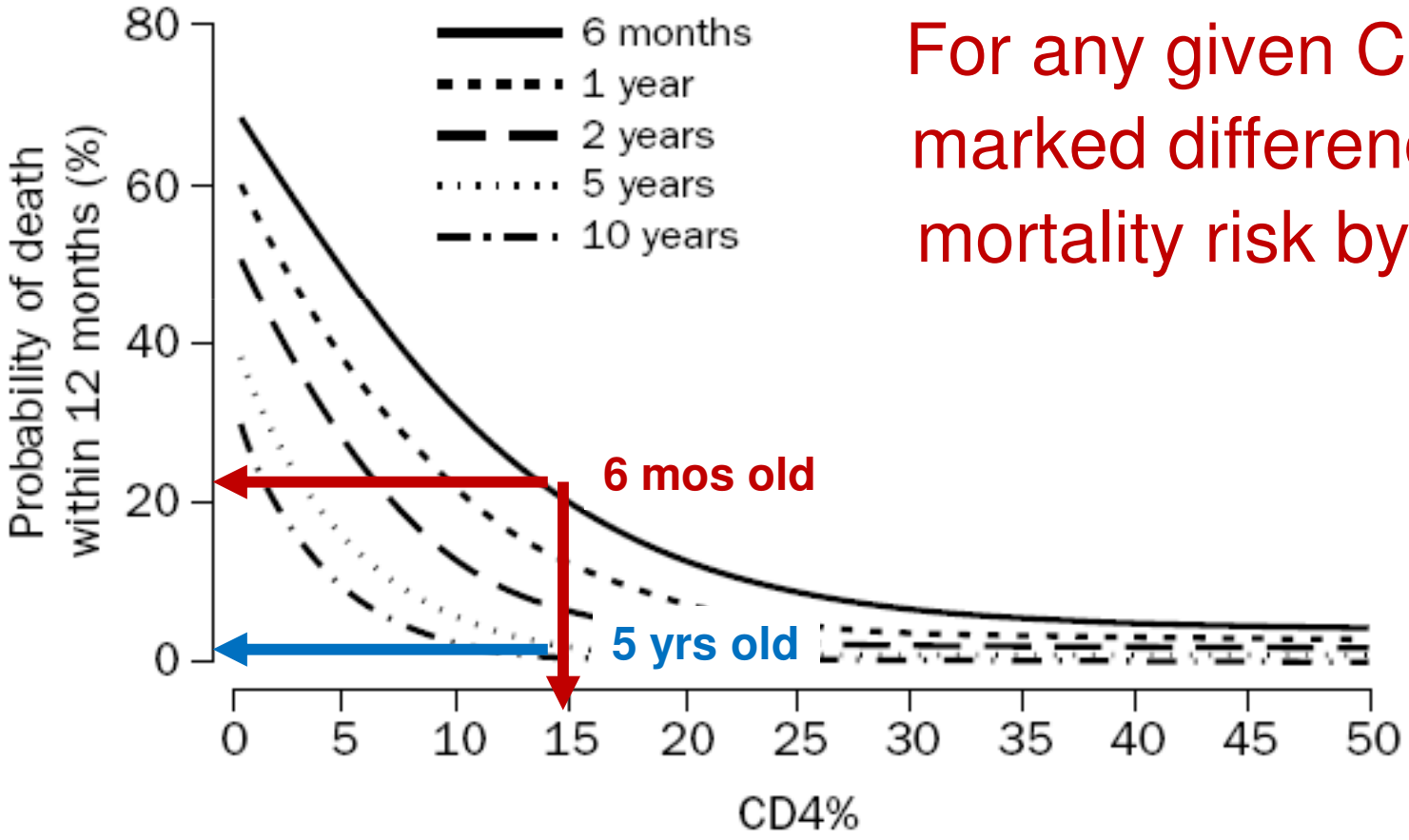
  - Progression lower but still high, surrogate marker better predictors but complicated by age-related change in CD4
  - Pediatric formulations needed, palatability issues

- Age >5 years

  - Progression more like adults, CD4 similar to adults
  - Generally can take solid tabs/caps but still need lower dose ped formulation

Relationship of Age, CD4% and Mortality Risk in Untreated HIV-Infected Children US/Europe (HPPMCS)

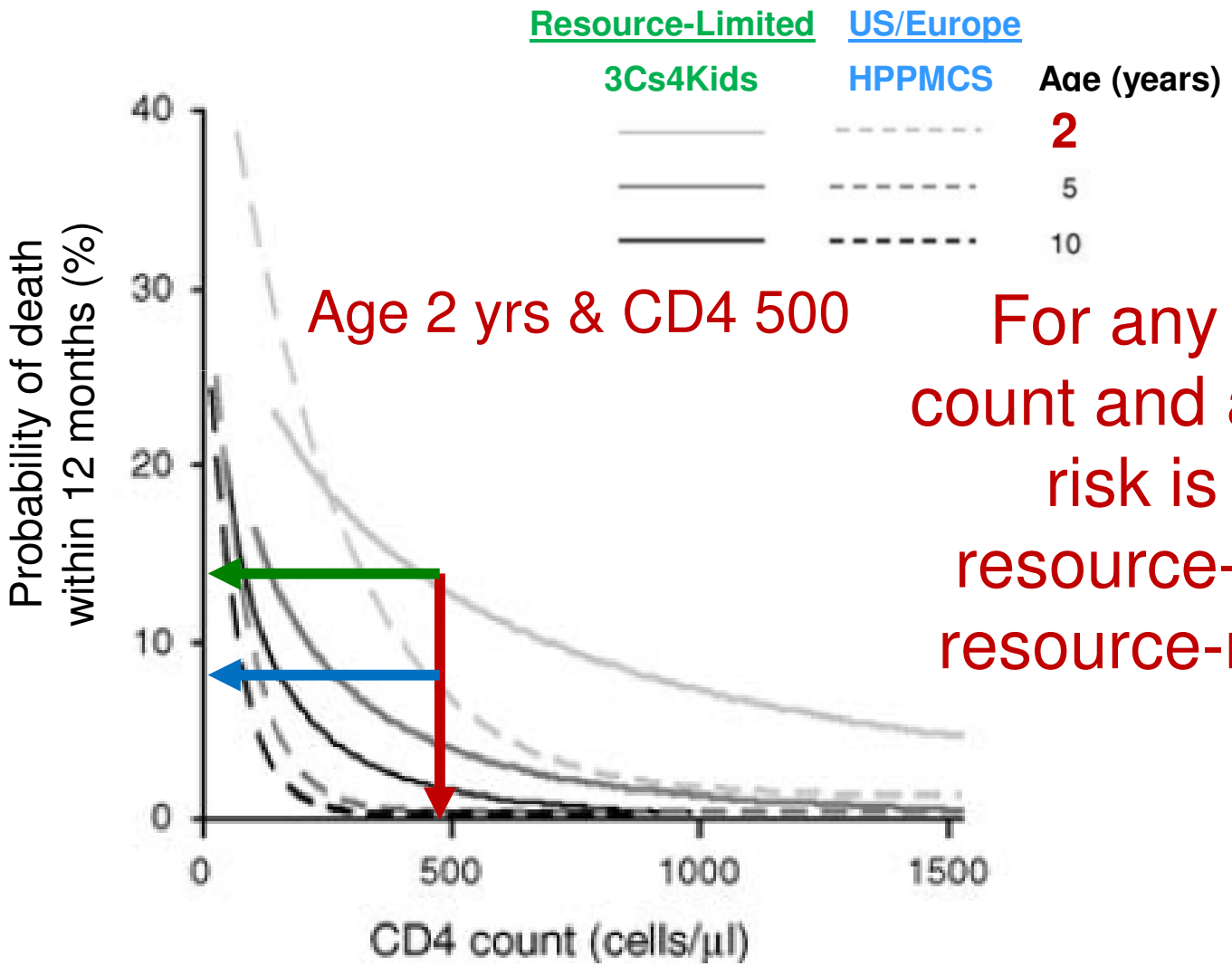
HPPMCS Lancet 2003;362:1605-11



For any given CD4% marked difference in mortality risk by age

Age, CD4, and Mortality in Resource-Limited (3Cs4kids) and Resource-Rich Countries (HPPMCS)

Cross Continent Collaboration for Kids AIDS 2008;22:97-105

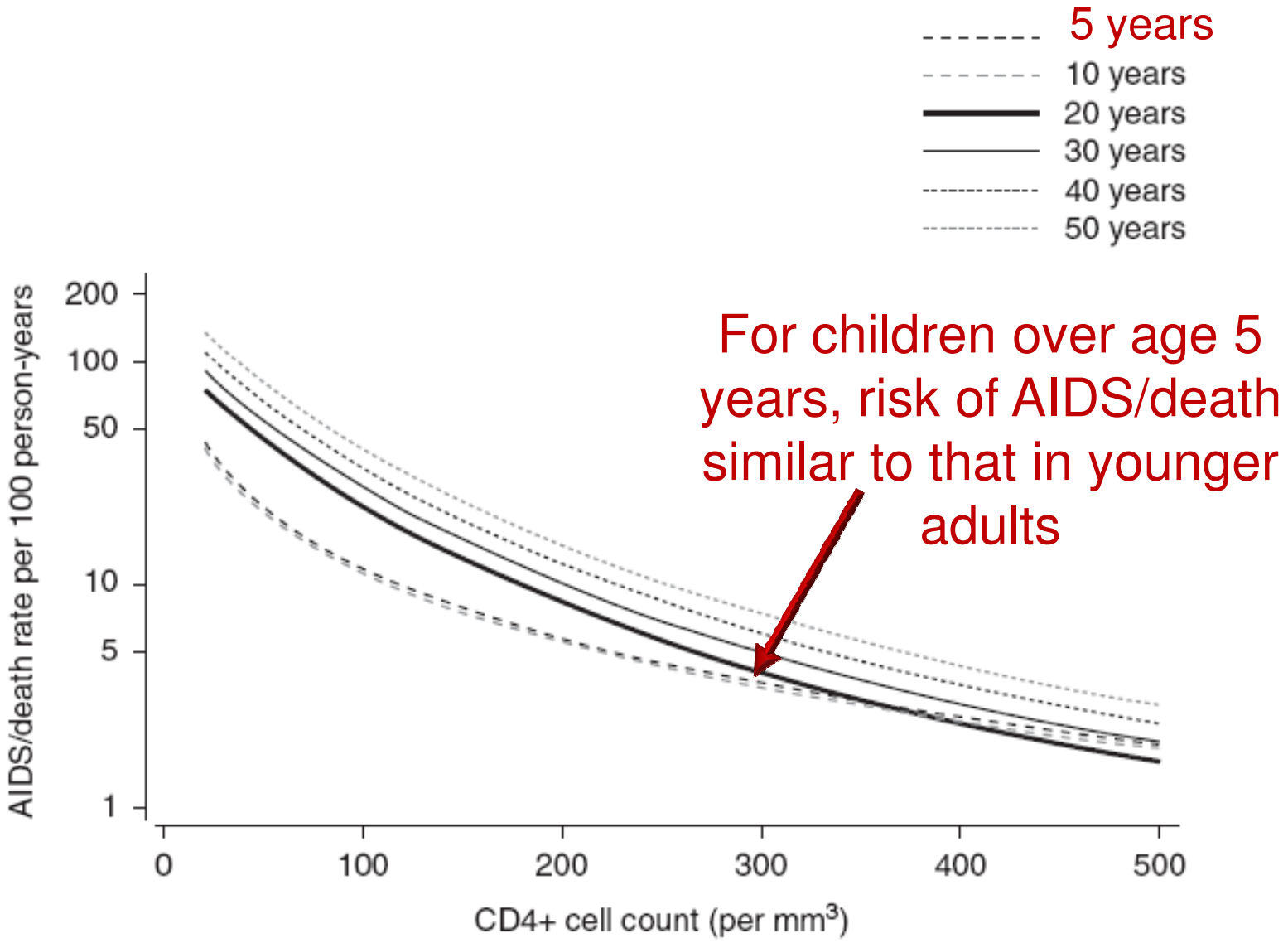


Age 2 yrs & CD4 500

For any given CD4 count and age, mortality risk is higher in resource-limited than resource-rich counties

Risk AIDS/Death by Age and CD4 Count: HPPMCS (children) and Cascade (adults)

Turkova A et al. Pediatr Drugs 2012;14:361-76



What Can We Learn From Resource Rich Countries?

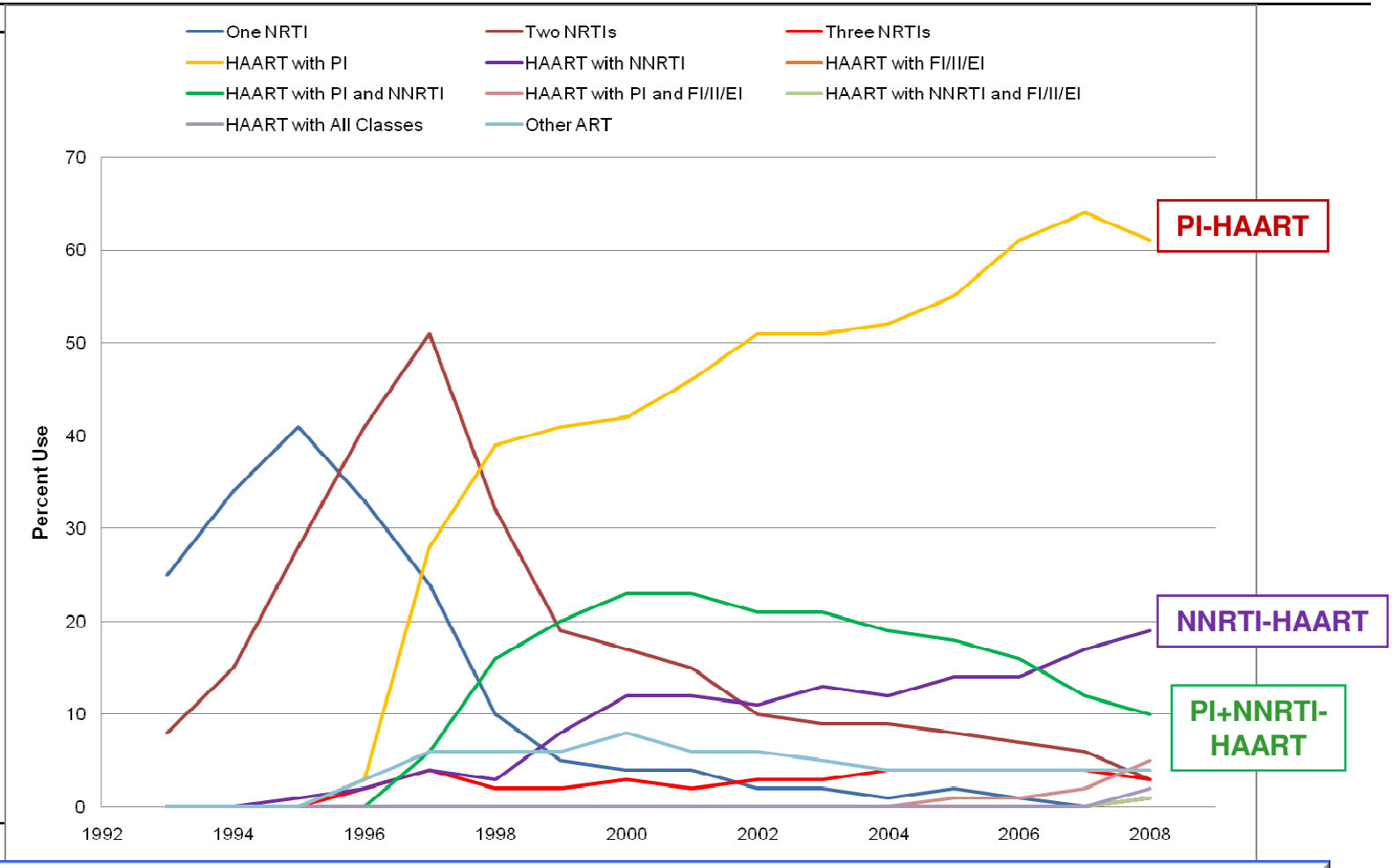
In the United States, the Majority of HIV-Infected Children Are Receiving Antiretroviral Therapy: PHACS/AMP Study

Van Dyke R et al. JAIDS 2011;57:165-73

451 perinatally-infected children from 15 US sites

At entry:

- Median age 12 yrs
- Median ART duration 11.4 yrs
- Median # individual ARVs taken: 7

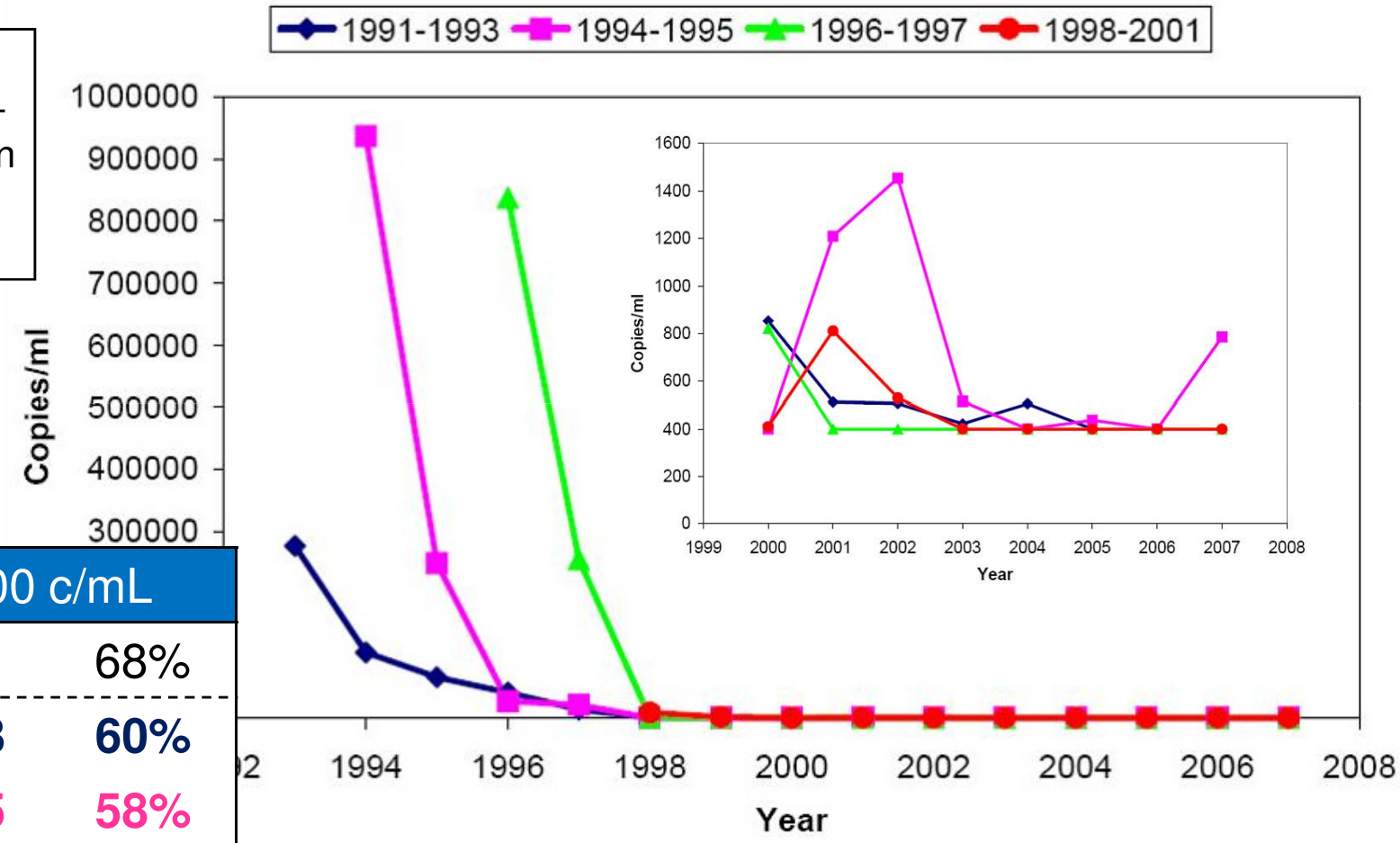


In 2008, 93% of HIV-infected children were on treatment

More Recent Birth Cohorts More Likely to Have Suppression of Viral Replication than Earlier Cohorts

Van Dyke R et al. JAIDS 2011;57:165-73

PHACS/AMP: 451 perinatally-infected children from 15 US sites



RNA <400 c/mL	
Overall	68%
1991-1993	**60%**
1994-1995	**58%**
1996-1997	**76%**
1998-2001	**78%**

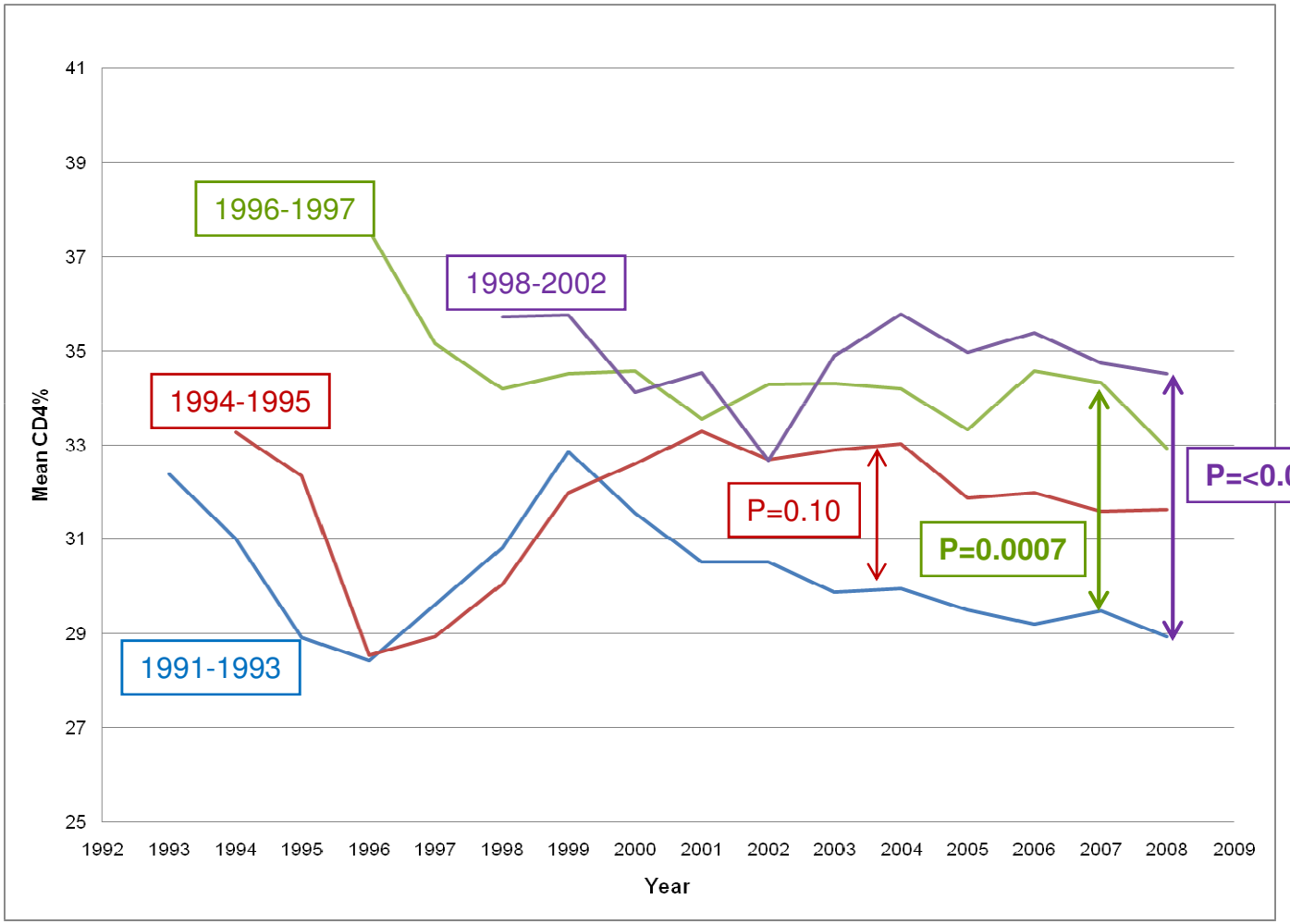
More Recent Birth Cohorts Have Better Immune Function (Higher CD4) Over Time than Earlier Cohorts

Van Dyke R et al. JAIDS 2011;57:165-73

PHACS/AMP
451 perinatally-infected children from 15 US sites

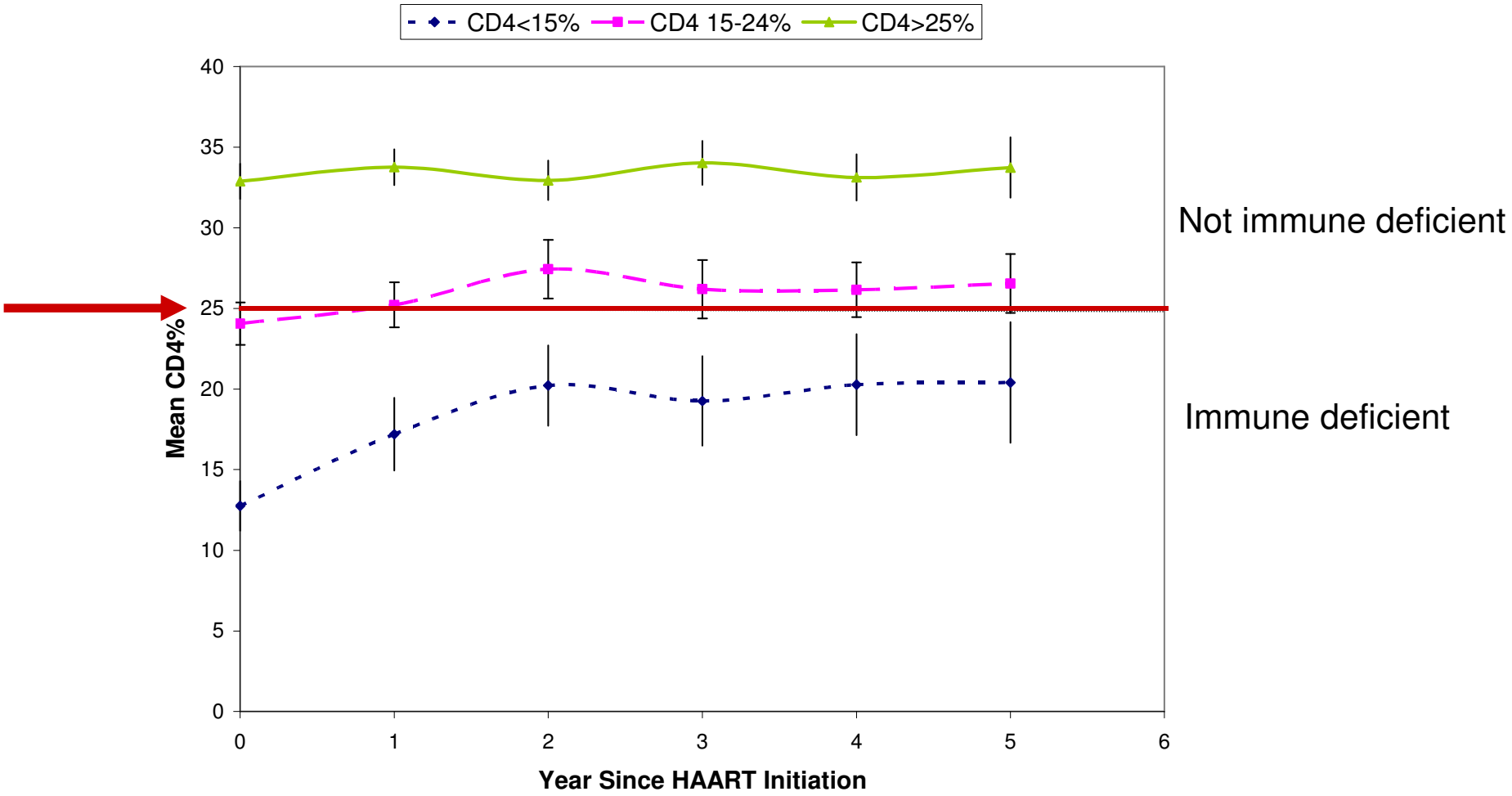
At entry:

- Median CD4 33%
- 78% had CD4 ≥25%



Recovery of Immune Status with Potent Therapy is Dependent on CD4% at Time Therapy is Initiated

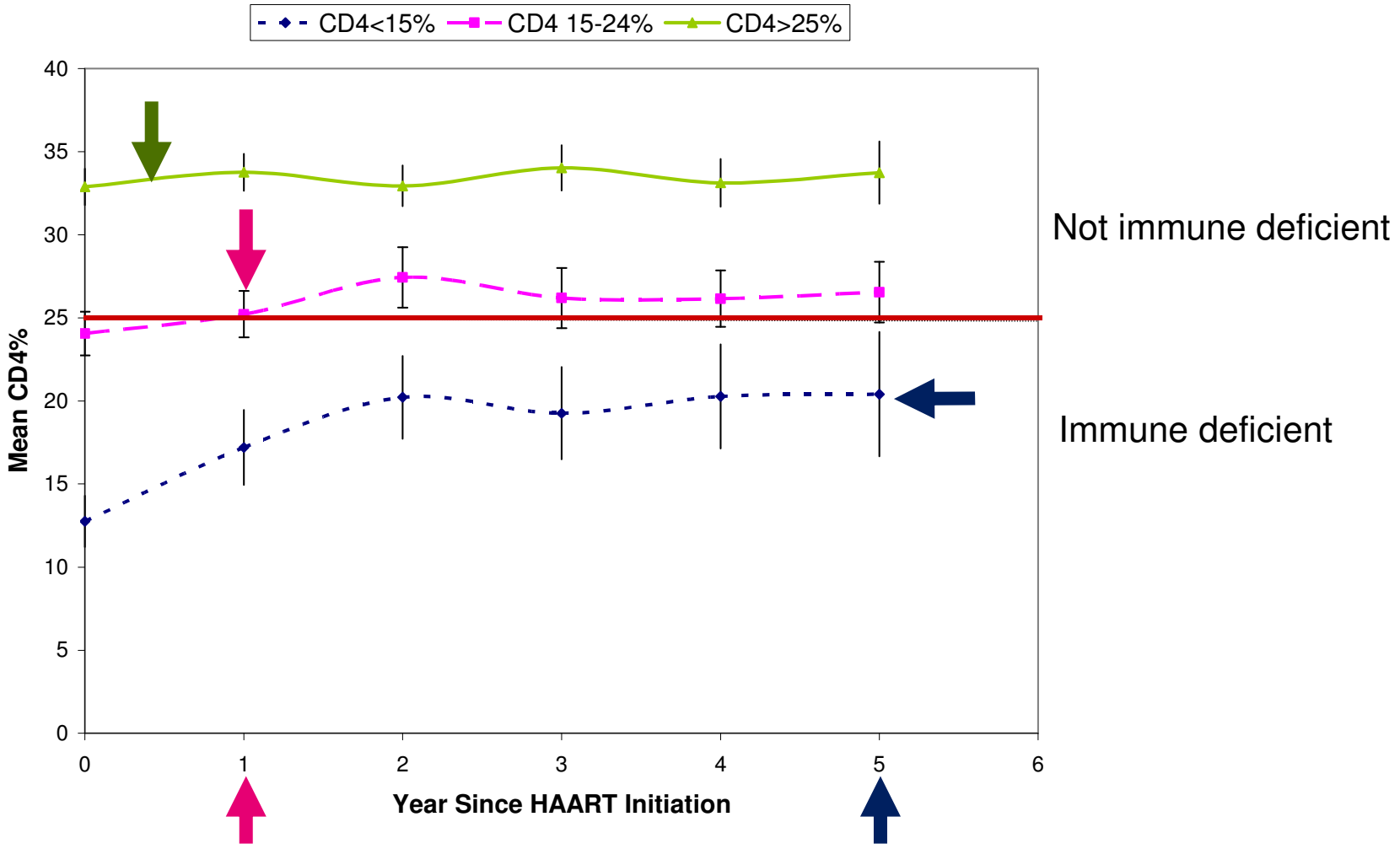
Patel K et al. Clin Infect Dis 2008;46:1751-60



1,236 children enrolled in PACTG 219 not on therapy at study initiation

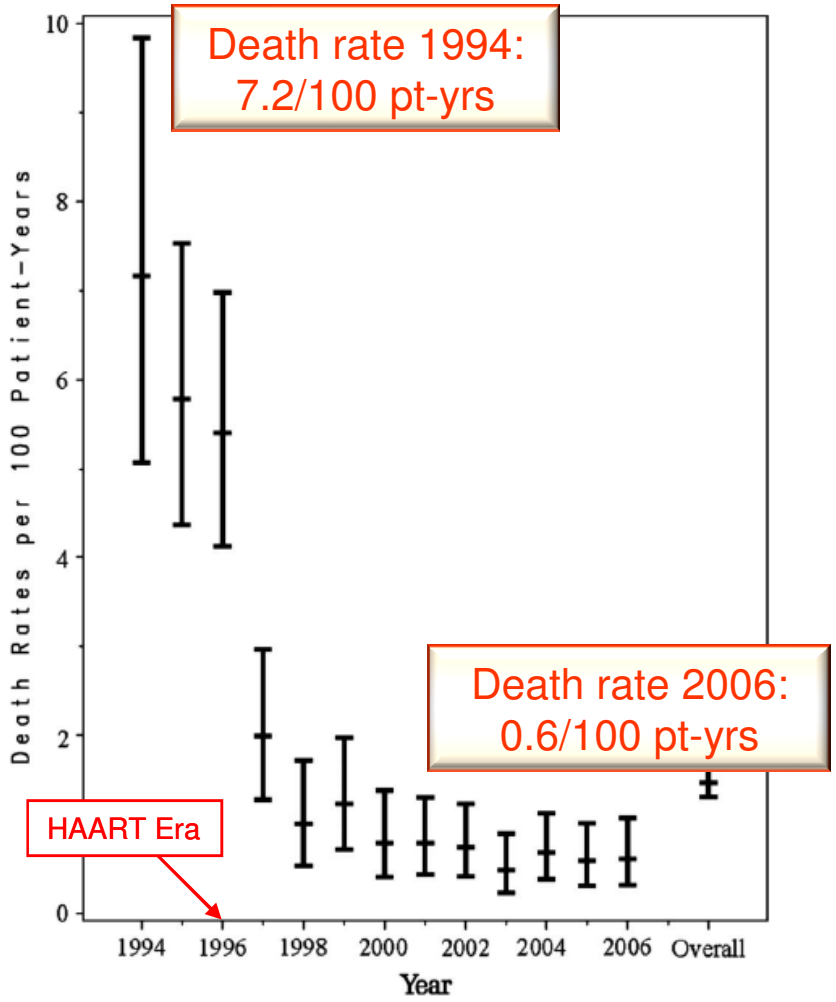
Recovery of Immune Status with Potent Therapy is Dependent on CD4% at Time Therapy is Initiated

Patel K et al. Clin Infect Dis 2008;46:1751-60

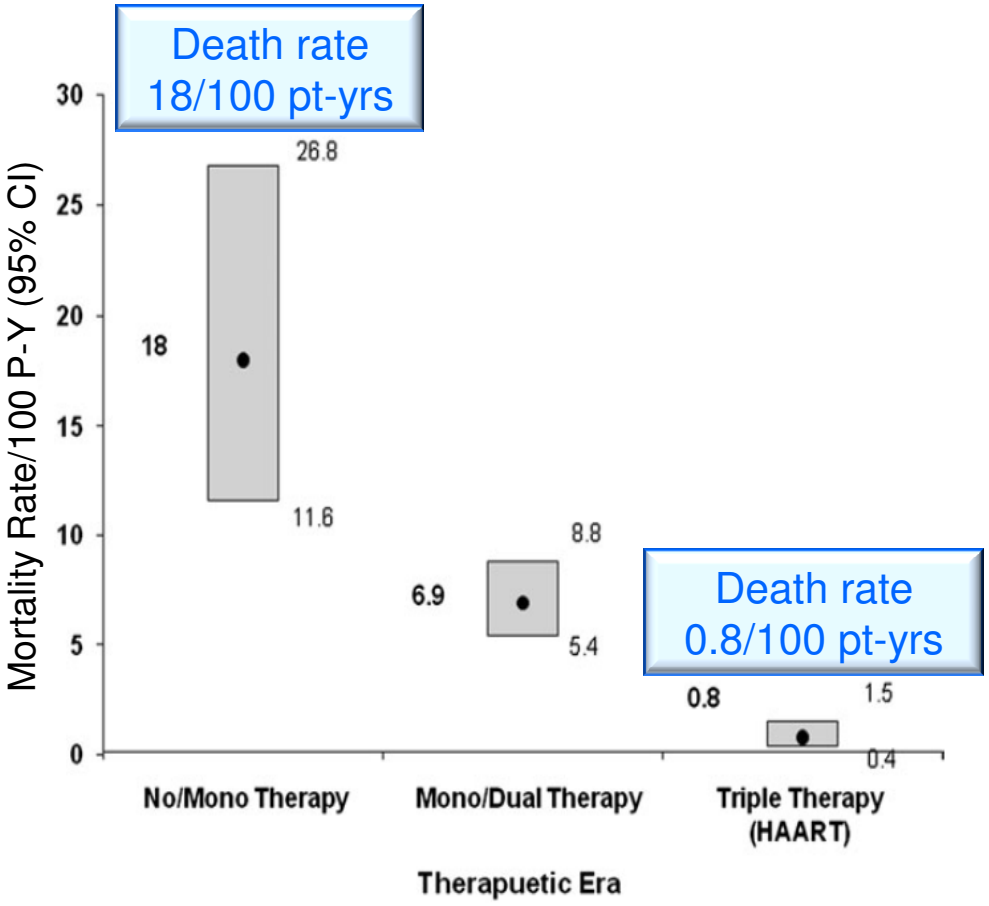


1,236 children enrolled in PACTG 219 not on HAART at study initiation

Significant Decline in Mortality in HIV-Infected Children Over Time Associated with Better Therapies



PACTG 219, observational study:
3,553 children
Brady M et al. JAIDS 2010;53:86-94



PACTS, birth cohort:
364 children
Kapogiannis B et al. CID 2011;53:1024-34

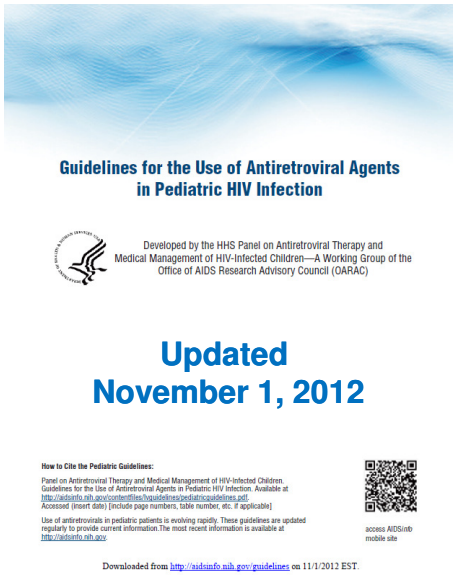


Table 15

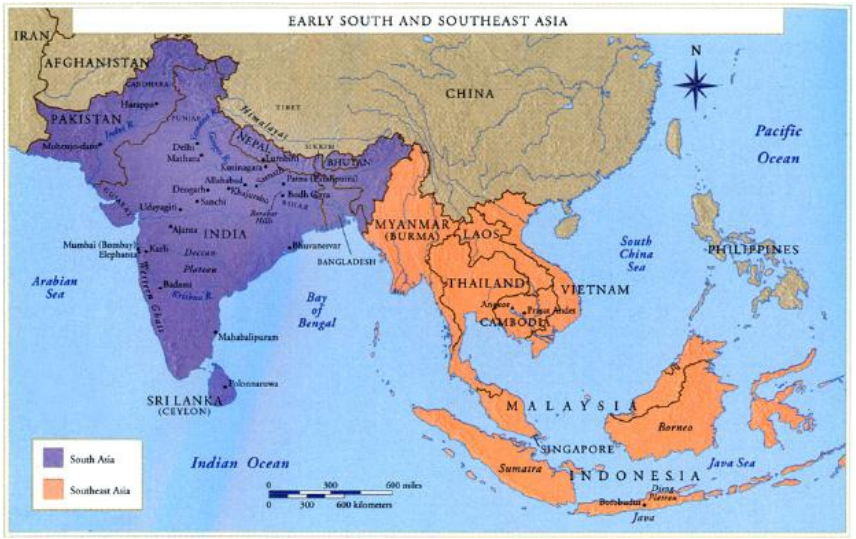
Schedule of Monitoring HIV-Infected Children Before and During ART

In U.S., ART is Individualized with Intensive Monitoring

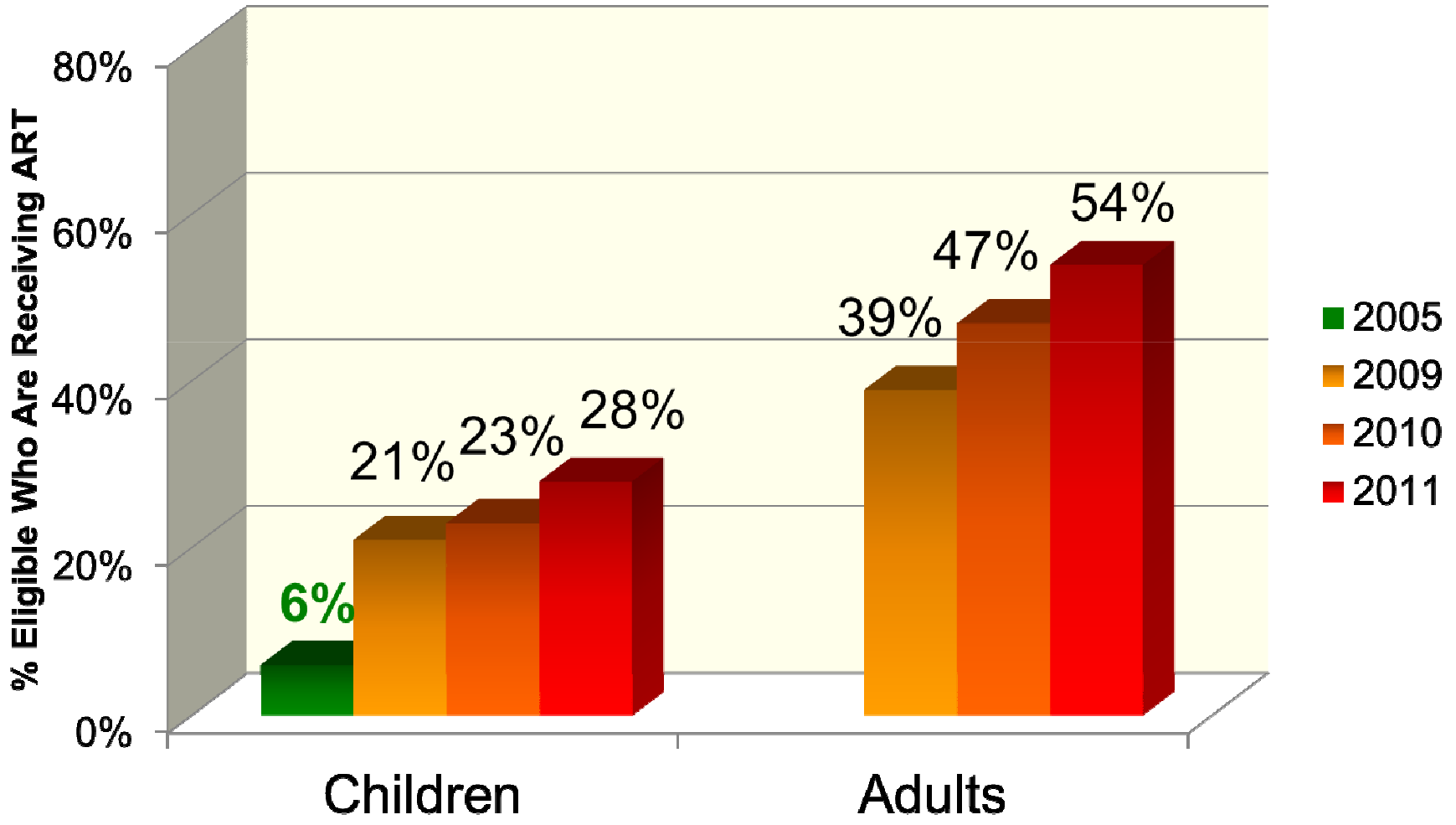
November 1, 2012 US Pediatric Guidelines

	Entry Into Care	Monitoring Pre-Therapy[1]	ART Initiation[1]	1–2 Weeks on Therapy[2]	4–8 Weeks on Therapy	Every 3–4 Months[3]	Every 6–12 Months	ARV Switch
Clinical History Physical Exam[2]	X	X	X	X	X	X	X	X
CBC w/ Differential	X	X	X		X	X		X
Chemistries[4]	X		X		X[4]	X		X
Electrolytes	X		X			X		X
Glucose	X		X			X		X
AST/ALT	X	X	X	X[5]	X[5]	X		X
Bilirubin	X		X			X		X
BUN/Creatinine	X	X	X			X		X
Albumin/Total Protein	X		X				X	X
Ca/Phosphate	X		X				X	X
CD4 Count/%	X	X	X		X[6]	X		X
HIV RNA	X	X	X	X[2]	X	X		X
Resistance Testing	X							X
Adherence Evaluation			X	X	X	X		X
Lipid Panel	X		X				X	
Urinalysis	X		X				X	

What About ART in More Resource-Limited Countries?

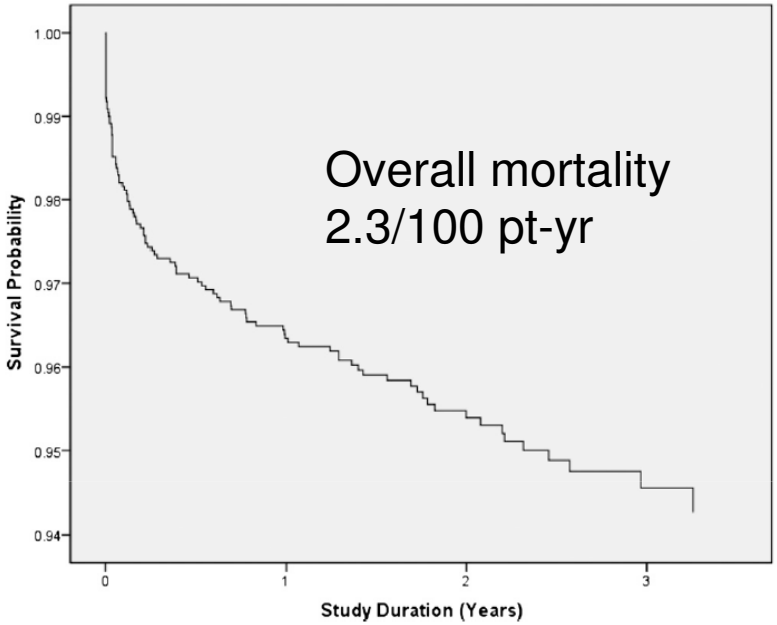


% Children and Adults Eligible for ART Who Are Receiving ART in Low and Middle-Income Countries, 2009-2011



WHO Global Reports 2005, 2009, 2010, 2011

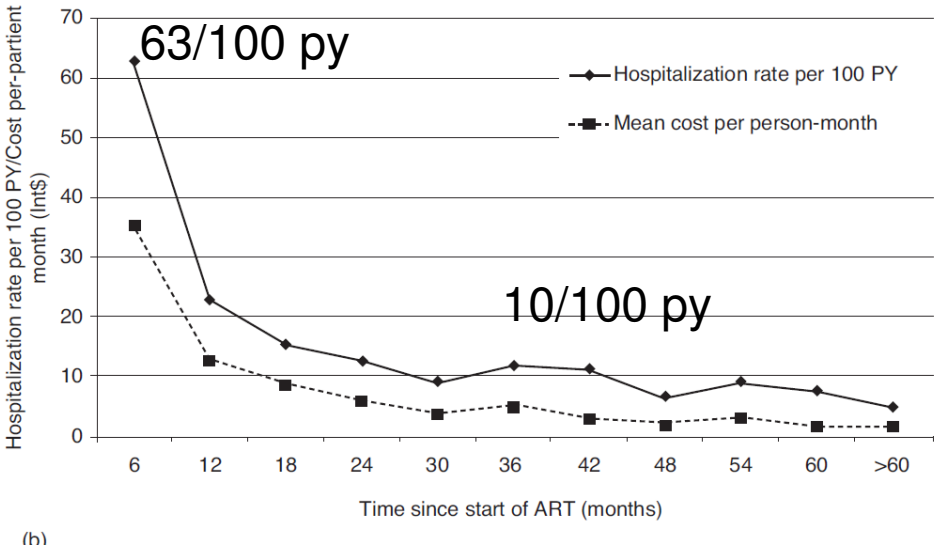
Clinical Response to ART in Children in Low Resource Countries is Good



Kabue et al. Pediatrics 2012;120:e591

- Significant declines in hospitalization/ cost in children on ART in Thailand; most occur in 1st yr ART.

- Significant declines in mortality with ART in children in Lesotho, Malawi, and Swaziland; most deaths (78%) in 1st year ART.



Collins et al. AIDS 2012;26:1943-52

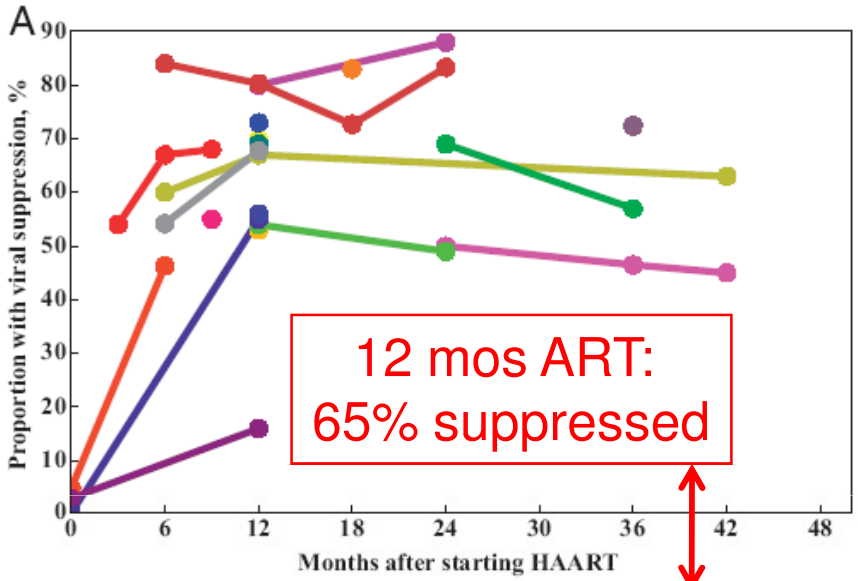
Viral Suppression in Developing vs Developed Countries

Peacock-Villada E et al. Pediatrics 2011;127:e423

Developing Countries

Mean age 5.7 yrs

Baseline RNA **5.5** log c/mL



- Burkina Faso (Hien, 2009)
- Cote d'Ivoire(Fassinou/Rouet, 2006)[a]
- Kenya (Song, 2007)[a]
- Kenya (Wamalwa, 2007)
- KwaZulu–Natal (Reddi, 2007)
- Mozanbique (Marazzi, 2006)
- Rwanda (van Griensven, 2008)
- South Africa (Barth, 2008)[a]
- South Africa (Eley, 2006)
- South Africa (Jaspan, 2008)
- South Africa (Smit,2 009)
- Zambia (Gupta, 2009)
- Uganda (Kamya, 2007)[a]
- Cambodia (Janssens, 2007)[a]
- China A (Zhang, 2007)[a]
- China B (Zhang, 2007)[a]
- Romania (Kline, 2007)
- Thailand (Puthanakit, 2007)[a]
- Haiti (George, 2007)

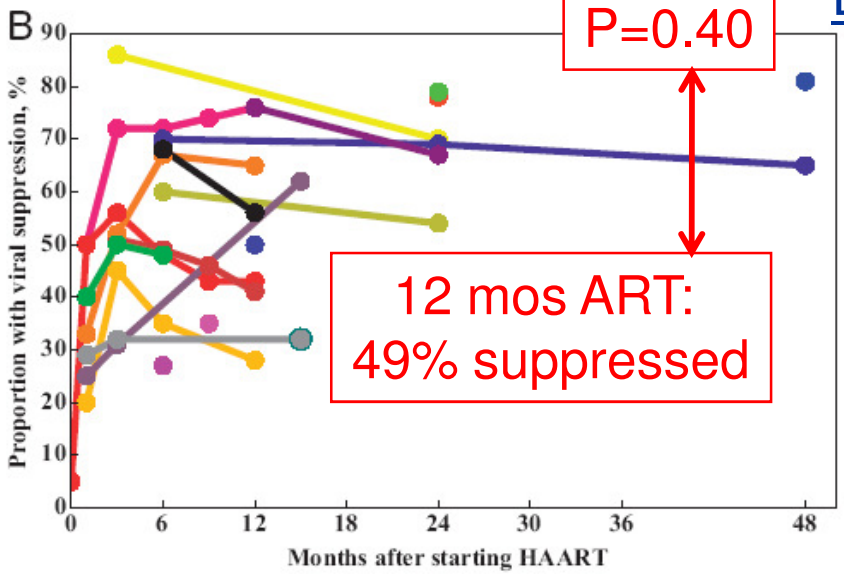
Majority studies used NNRTI-based regimens

P=0.40

Developed Countries

Mean age 6.7 yrs

Baseline RNA **4.7** log c/mL



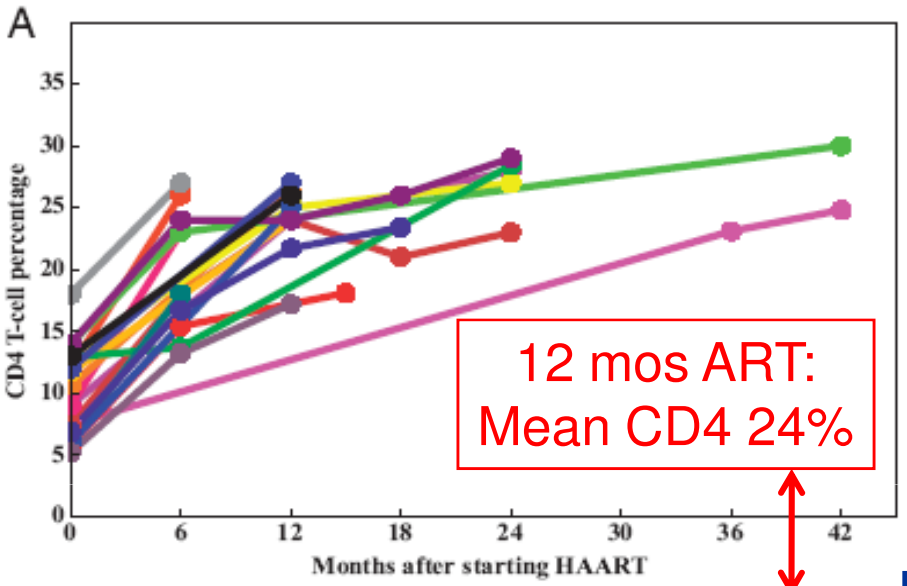
- US (Krogstad, 1999)
- US (Watson, 1999)
- US (Starr, 1999/Spector, 2000)[a]
- US (Yogev, 2002)[a]
- US (Krogstad,2002)[a]
- US (Melvin, 2002)
- US A (King, 2005)[a]
- US B (King, 2005)[a]
- US (McKinney, 2007)[a]
- UK, Ireland (Judd, 2007)
- UK, Ireland (Walker, 2004)
- France (Teglas, 2001)
- France (Thuret, 1999)
- Germany (Wintergerst, 2008)[a]
- Netherlands (Fraaij, 2005/van Ross., 2002)[a]
- Netherlands (Scherpbier, 2007)
- Switzerland A (Nadal, 2000)
- Switzerland B (Nadal, 2000)
- Switzerland (Rudin, 2008)[a]
- PENTA, 2002[a]

Majority studies used PI-based regimens

CD4% Levels Post ART in Developing vs Developed Countries

Peacock-Villada E et al. Pediatrics 2011;127:e423

Baseline CD4% **12%**



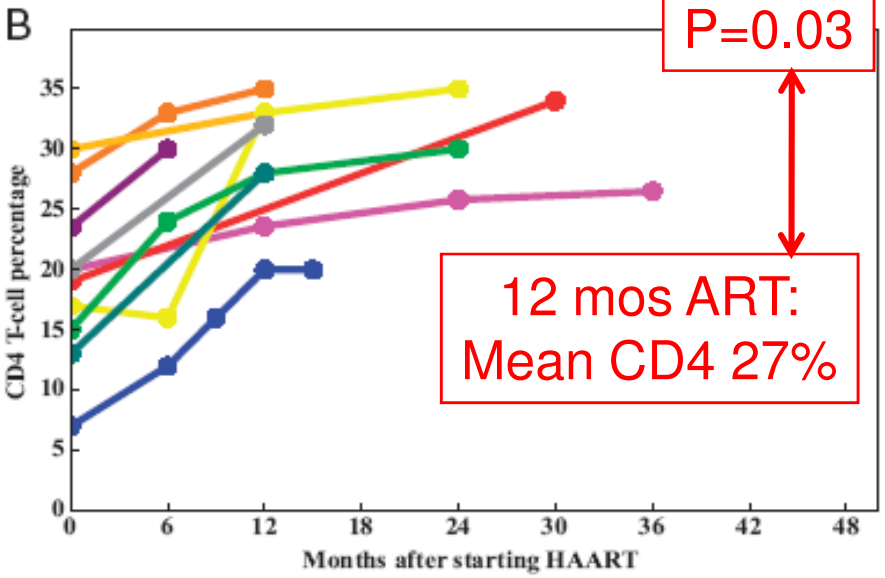
12 mos ART: Mean CD4 24%

Developing Countries

- Burkina Faso (Hien, 2009)
- Cote d'Ivoire (Rouet, 2006)
- Kenya (Nyandiko, 2006)
- Kenya (Wamalwa, 2007)
- KwaZulu–Natal (Reddi, 2007)
- Mozambique (Vaz, 2009)
- South Africa (Barth, 2008)
- South Africa (Eley, 2006)
- South Africa (Jaspan, 2008)
- South Africa (Smit, 2009)
- Tanzania (Blè, 2007)
- Zambia (Bolton–Moore, 2007)
- Zambia (Walker, 2007)
- Cambodia (Janssens, 2007)
- Camboida (Myung, 2007)
- India (Rajasekaran, 2009)
- Thailand (Puthanakit, 2007)
- Brazil (Diniz, 2009)
- Haiti (George, 2007)
- Haiti (Severe, 2005)

P=0.03

Baseline CD4% **23%**



12 mos ART: Mean CD4 27%

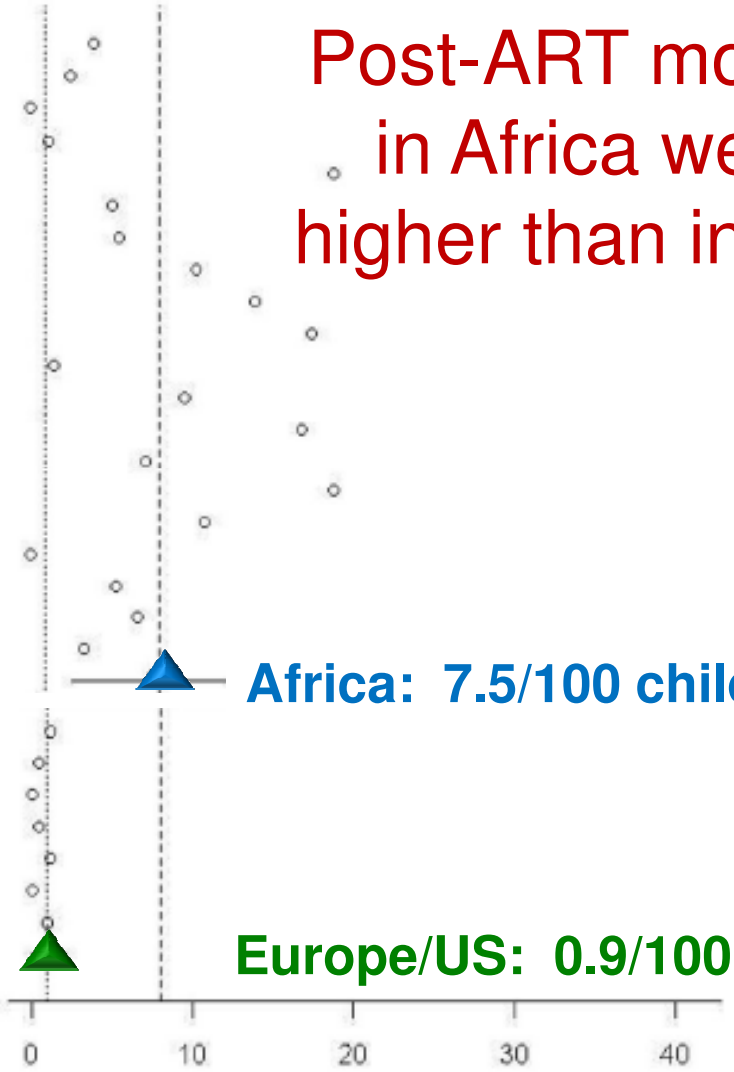
Developed Countries

- US (Krogstad, 1999)
- US (Soh, 2003)
- US (Melvin, 2002)
- US (Rosenblatt, 2005)
- US (Starr, 2000)
- US (McKinney, 2007)
- UK, Ireland (Walker, 2004)
- France (Thuret, 1999)
- Switzerland A (Nadal, 2000)
- Switzerland B (Nadal, 2000)

Mortality on ART in Developing vs Developed Countries

Peacock-Villada E et al. Pediatrics 2011;127:e423

Country and First Author	N=	Time, mo
Burkina Faso (Hien)	52	12
Kenya (Nyandiko)	279	Med. 34
Kenya (Song)	29	15
Kenya (Van Winghem)	648	12
Kenya (Wamalwa)	67	6
Lesotho (Cohen)	283	12
Lesotho (Leyenaar)	284	14
Malawi	436	6
Malawi	233	12
Mozambique (Marazzi)	297	6
Rwanda (van Griensven)	315	24
South Africa (Barth)	66	12
South Africa (Eley)	407	12
South Africa (Jaspan)	391	12
South Africa (Jooste)	100	6
South Africa (Smit)	615	12
Tanzania (Blé)	59	12
Uganda (Kamya)	250	12
Zambia (Bolton-Moore)	2938	36
Zambia (Walker)	93	24
Africa Mean		
PENTA	103	48wk
Denmark (Bracher)[a]	49	108
France (Thuret)[a]	22	Med. 16
Netherlands (Fraaij)[a]	31	48
Switzerland (Rudin)[a]	133	66
USA (McKinney)	27	24
USA (Patel)[a]	866	Med. 70
Europe/US Mean		

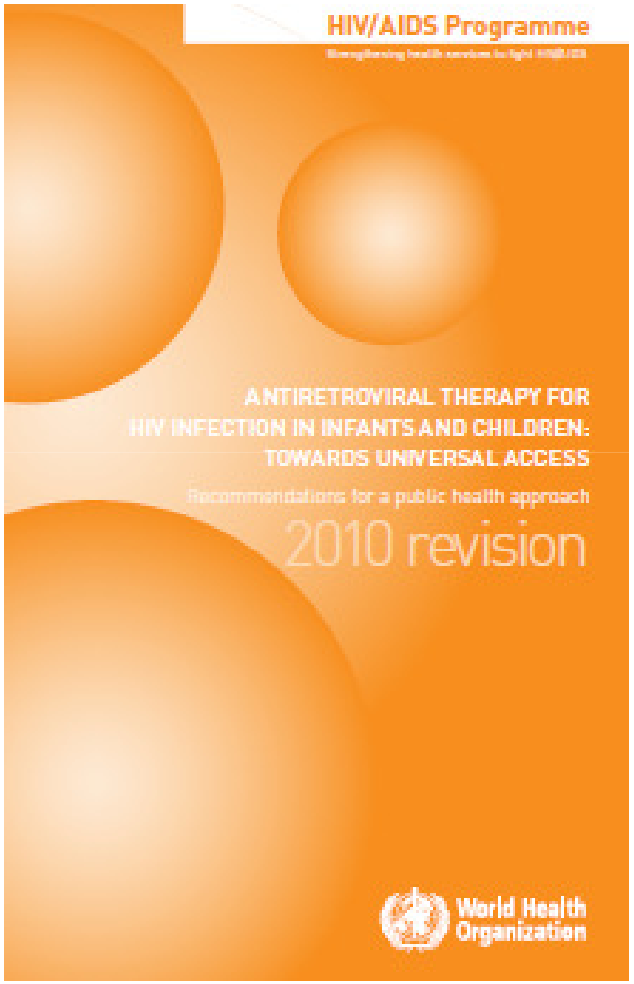


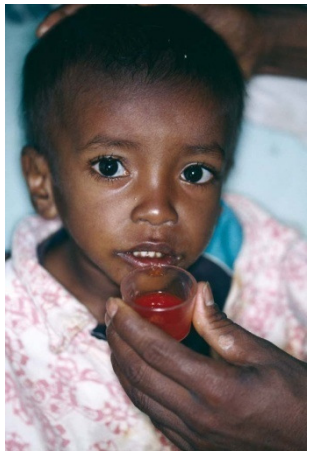
Post-ART mortality rates in Africa were 8-fold higher than in US/Europe

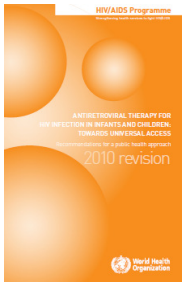
Africa: 7.5/100 child-years

Europe/US: 0.9/100 child-years

When to Start







WHEN TO TREAT: Infants - <2 Years
2010 WHO Pediatric HIV Recommendations

Table 6: Recommendations for initiating ART in infants and children; revised in 2010

Age	Infants and children <24 months of age[a,b]	≥24 months of age to 59 months of age	Five years of age or older
%CD4+	All[c]	≤25	NA
Absolute CD4	All[c]	≤750 cells/mm^3	≤350 cells/mm^3 (As in adults)

Table 7: Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and immunological markers

	Clinical stage	Immunological
<24 months	Treat all	
>24 months	Stage 4[a]	Treat all[b]
	Stage 3[a]	Treat all
	Stage 2	Treat if CD4 below age-adjusted threshold
	Stage 1	Don't treat if no CD4 available:

ORIGINAL ARTICLE

Early Antiretroviral Therapy and Mortality among HIV-Infected Infants

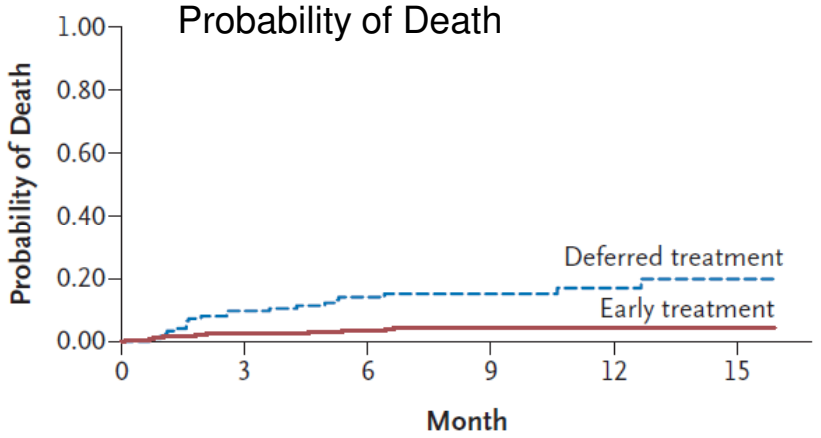
Avy Violari, F.C.Paed., Mark F. Cotton, M.Med., Ph.D., Diana M. Gibb, M.D., Abdel G. Babiker, Ph.D., Jan Steyn, M.Sc., Shabir A. Madhi, F.C.Paed., Ph.D., Patrick Jean-Philippe, M.D., and James A. McIntyre, F.R.C.O.G., for the CHER Study Team*

N Engl J Med 2008;359:2233-44.

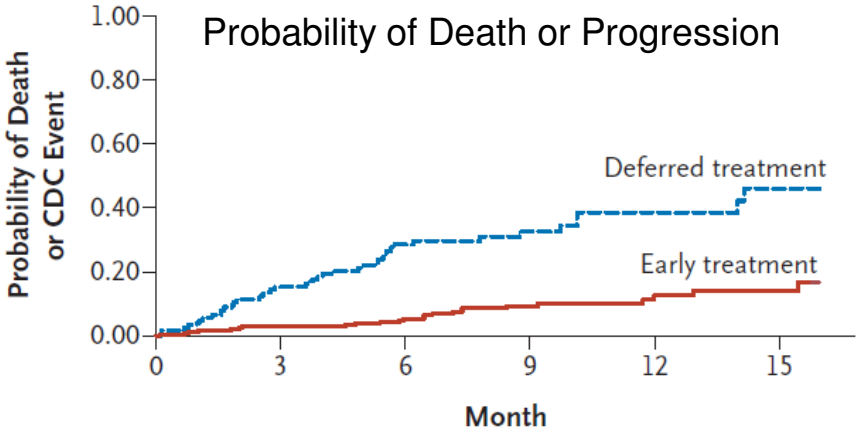
Early Treatment in Infants Reduces Disease Progression and Death: CHER Trial

Compared starting treatment in asymptomatic HIV+ infants with CD4 ≥25% aged <4 months vs deferring until met standard criteria

75% Reduction in Mortality:
4% vs 16% for
Early vs Deferred ART



77% Reduction in Death/ Progression:
6% vs 26% for
Early vs Deferred ART



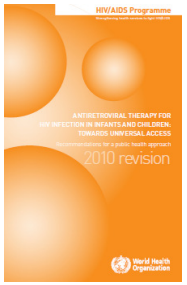
Early HAART in HIV-Infected Infants Associated with Improved Neurodevelopmental Outcome: CHER and Control Children

Laughton B et al. AIDS 2012;26:1685-90

Griffiths Mental Development Scales given at median age 11 mos to deferred vs early patients, HIV-exposed uninfected, & HIV-unexposed children

Characteristic	Deferred ART	Early ART	HIV-exposed uninfected	HIV-unexposed	P Value Defer vs Early
Number	26	64	28	34	
Mean Motor	88.9	97.7 ↔	105.3 ↔	101.6	<0.01
Mean General	100.1	106.3 ↔	105.6 ↔	106.9	0.02

CHER Trial: Enrolled HIV-infected infants <12 weeks of age and randomized to deferred vs immediate ARV.



WHEN TO TREAT: ≥2 Years
2010 WHO Pediatric HIV Recommendations

Table 6: Recommendations for initiating ART in infants and children; revised in 2010

Age	Infants and children <24 months of age[a,b]	≥24 months of age to 59 months of age	Five years of age or older
%CD4+	All[c]	≤25	NA
Absolute CD4	All[c]	≤750 cells/mm^3	≤350 cells/mm^3 (As in adults)

Table 7: Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and immunological markers

	Clinical stage	Immunological
<24 months	Treat all	
>24 months	Stage 4[a]	Treat all[b]
	Stage 3[a]	Treat all
	Stage 2	Treat if CD4 below age-adjusted threshold Don't treat if no CD4 available:
	Stage 1	

PREDICT Study Design

Pediatric **R**andomized of **E**arly vs **D**eferred **I**nitiation in **C**ambodia and **T**hailand

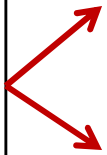
Puthanakit T et al. Lancet 2012;12:933-41

Children age 1-12 yrs with CD4 15-24% and CDC A or B (n=300)

Baseline (mean):

Age 6.4 yr

CD4 20%/619



Immediate (Early) ART (N=149)

Deferred ART (CD4 <15%* or CDC C) (N=150)

*April 2009: Immunological Criteria to start ART in children aged from 1-3 years change to CD4 < 20%

Primary Endpoint

AIDS-free survival at week 144 and neurodevelopmental outcome

Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial

Thanyawee Puthanakit, Vonthanak Saphonn, Jintanat Ananworanich, Pope Kosalaraksa, Rawiwan Hansudewechakul, Ung Vibol, Stephen J Kerr, Suparat Kanjanavanit, Chaiwat Ngampiyaskul, Jurai Wongsawat, Wicharn Luesomboon, Nicole Ngo-Giang-Huong, Kea Chettra, Theshinee Cheunyam, Tulathip Suwarnlerk, Sasiwimol Ubolyam, William T Shearer, Robert Paul, Lynne M Mofenson, Lawrence Fox, Matthew G Law, David A Cooper, Praphan Phanuphak, Mean Chhi Vun, Kiat Ruxrungtham, on behalf of the PREDICT Study Group

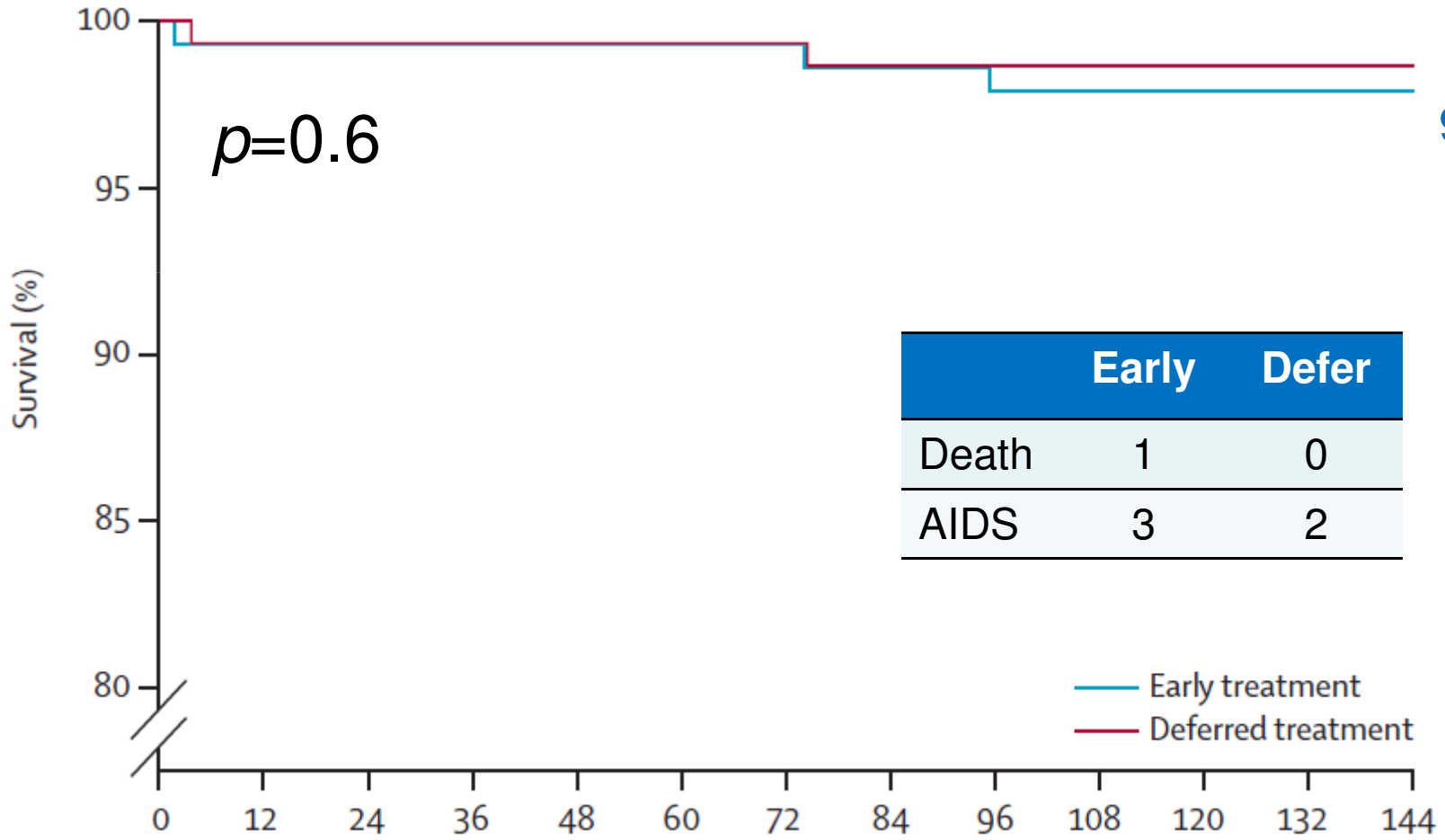
Lancet Infect Dis 2012;12;933-41

PREDICT Study: AIDS-Free Survival

AIDS-free survival week 144

98.7%

97.9%



	Early	Defer
Death	1	0
AIDS	3	2

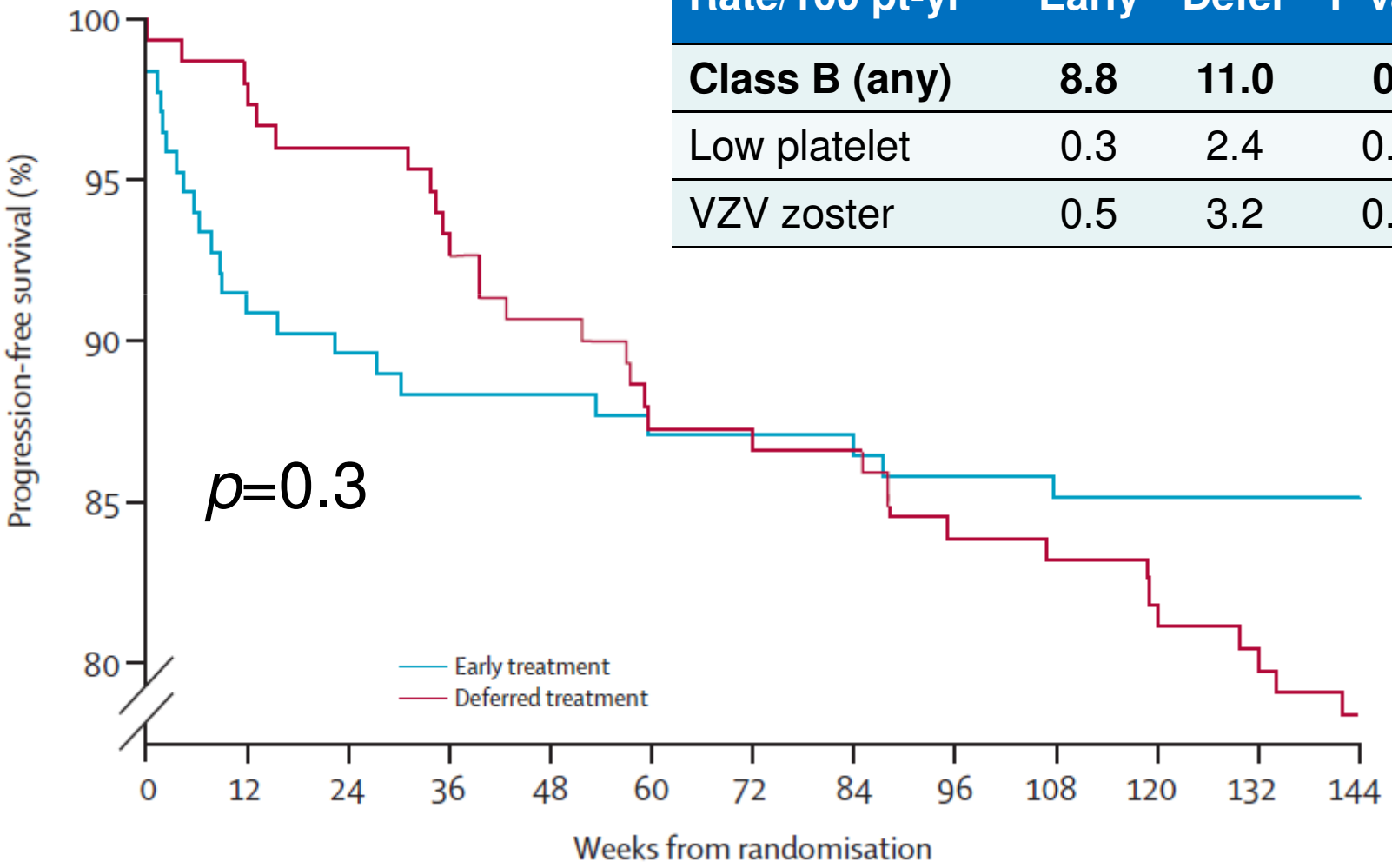
Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial

Thanyawee Puthanakit, Vonthanak Saphonn, Jintanat Ananworanich, Pope Kosalaraksa, Rawiwan Hansudewechakul, Ung Vibol, Stephen J Kerr, Suparat Kanjanavanit, Chaiwat Ngampiyaskul, Jurai Wongsawat, Wicharn Luesomboon, Nicole Ngo-Giang-Huong, Kea Chettra, Theshinee Cheunyam, Tulathip Suwarnlerk, Sasiwimol Ubolyam, William T Shearer, Robert Paul, Lynne M Mofenson, Lawrence Fox, Matthew G Law, David A Cooper, Praphan Phanuphak, Mean Chhi Vun, Kiat Ruxrungtham, on behalf of the PREDICT Study Group

Lancet Infect Dis 2012;12;933-41

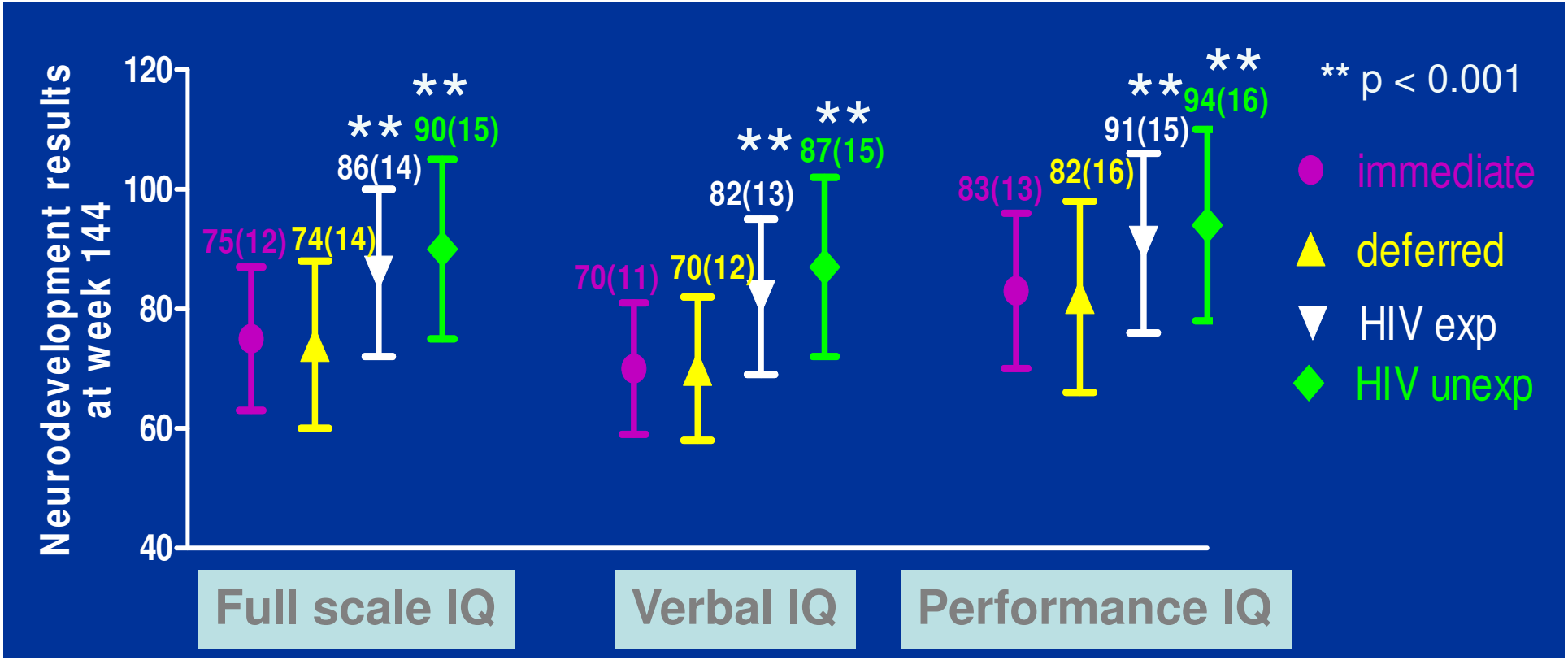
PREDICT Study: Death or Progression to CDC Class B or C

Rate/100 pt-yr	Early	Defer	P value
Class B (any)	**8.8**	**11.0**	**0.3**
Low platelet	0.3	2.4	0.03
VZV zoster	0.5	3.2	0.02



Intelligence Scores Were Not Different Between Immediate vs. Deferred ART

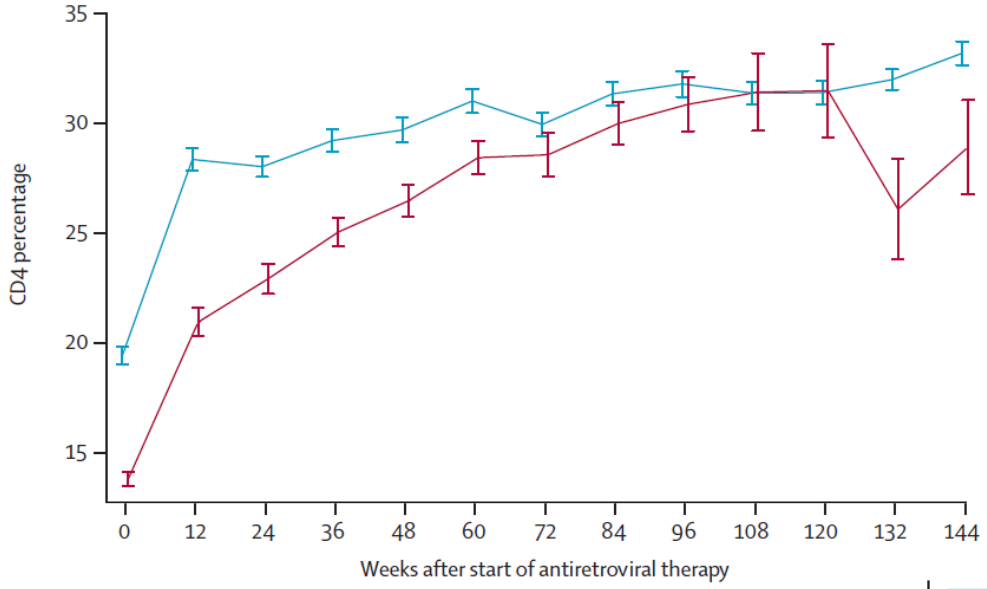
Puthanakit T. 19th CROI, Seattle, WA, March 2012 (Abs 24)



Intelligence Scores Were Lower In HIV-Infected Children Compared to HIV-Uninfected Controls

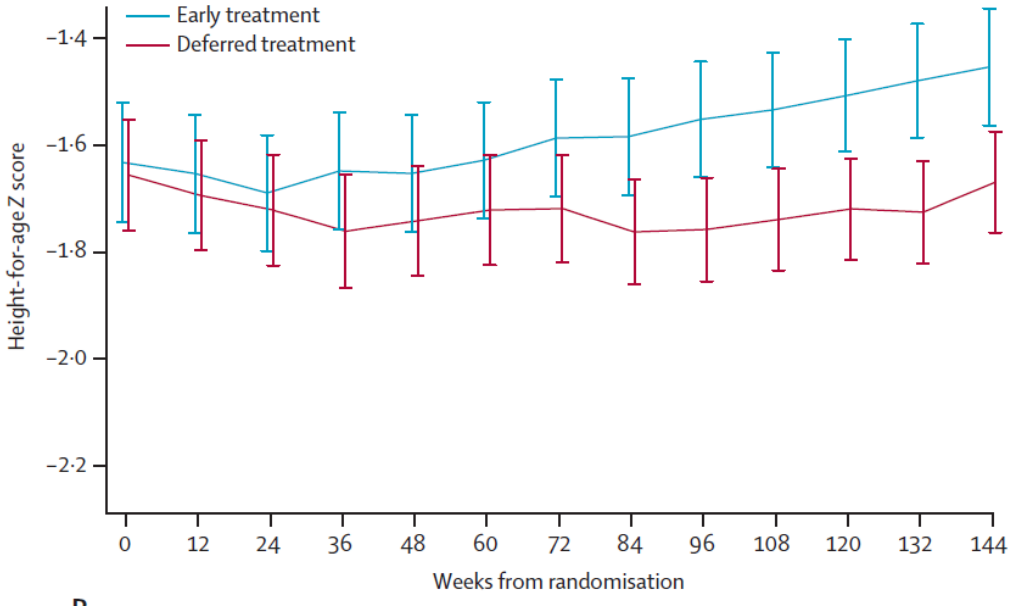
CD4 and Height Better with Early ART

Puthanakit T et al. Lancet Infect Dis 2012;12:933-41



- Median CD4 at week 144 was 33.2% in early vs 24.8% in deferred arms (p<0.0001)

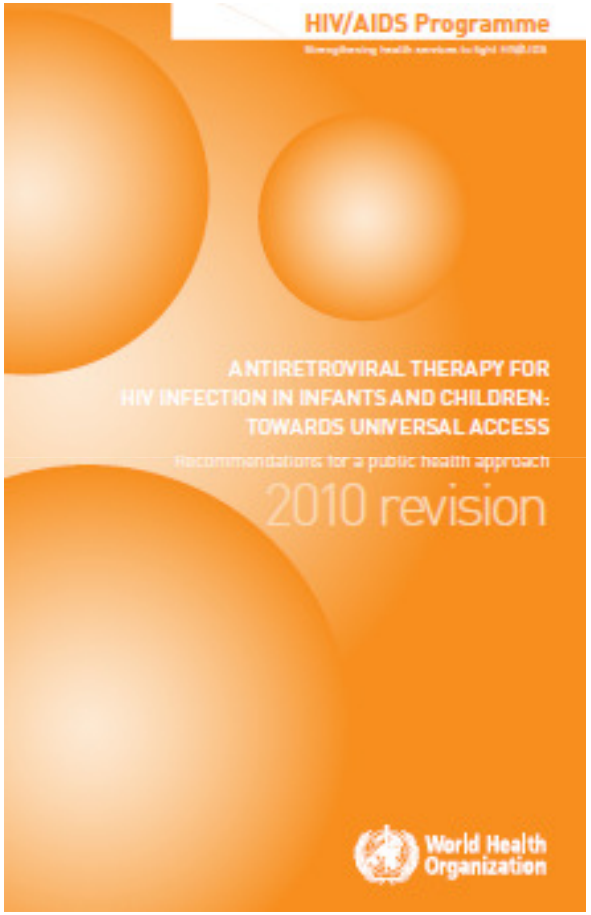
- While no difference btn arms for weight, mean height gain per year was 5.4 cm in early vs 4.9 cm in deferred arm (p=0.001)

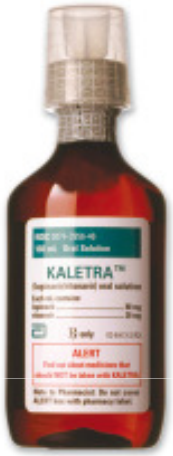


PREDICT – ART Response

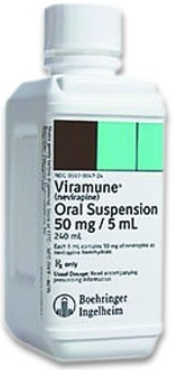
- Over the 3 year study period, 46% of deferred arm children started ART (96% for immunologic criteria).
- For children with at least 48 weeks of ART, no difference in rates of viral suppression between arms: 81% of early vs 85% of deferred children had RNA <50 copies/mL.
- Overall 9% in the early vs 6% in the deferred group switched to 2nd line (p=0.59).
- 17% of children in the early vs 10% in the deferred arm had grade 3 or 4 events secondary to ART (p=0.19)

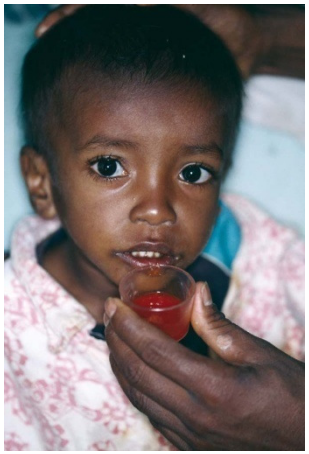
What to Start

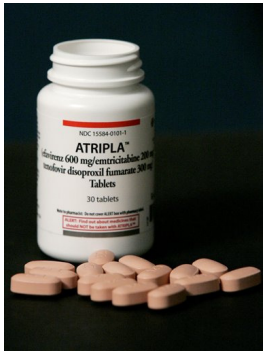




80 mg/20 mg/mL Kaletra oral solution [lopinavir/ritonavir]

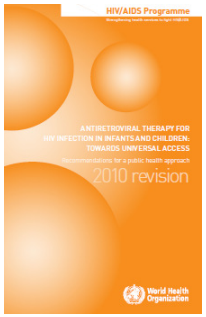






Tenofovir

50 mg/5mL Retrovir syrup



Preferred First-Line Pediatric ARV Regimens: 2010 WHO Pediatric HIV Recommendations

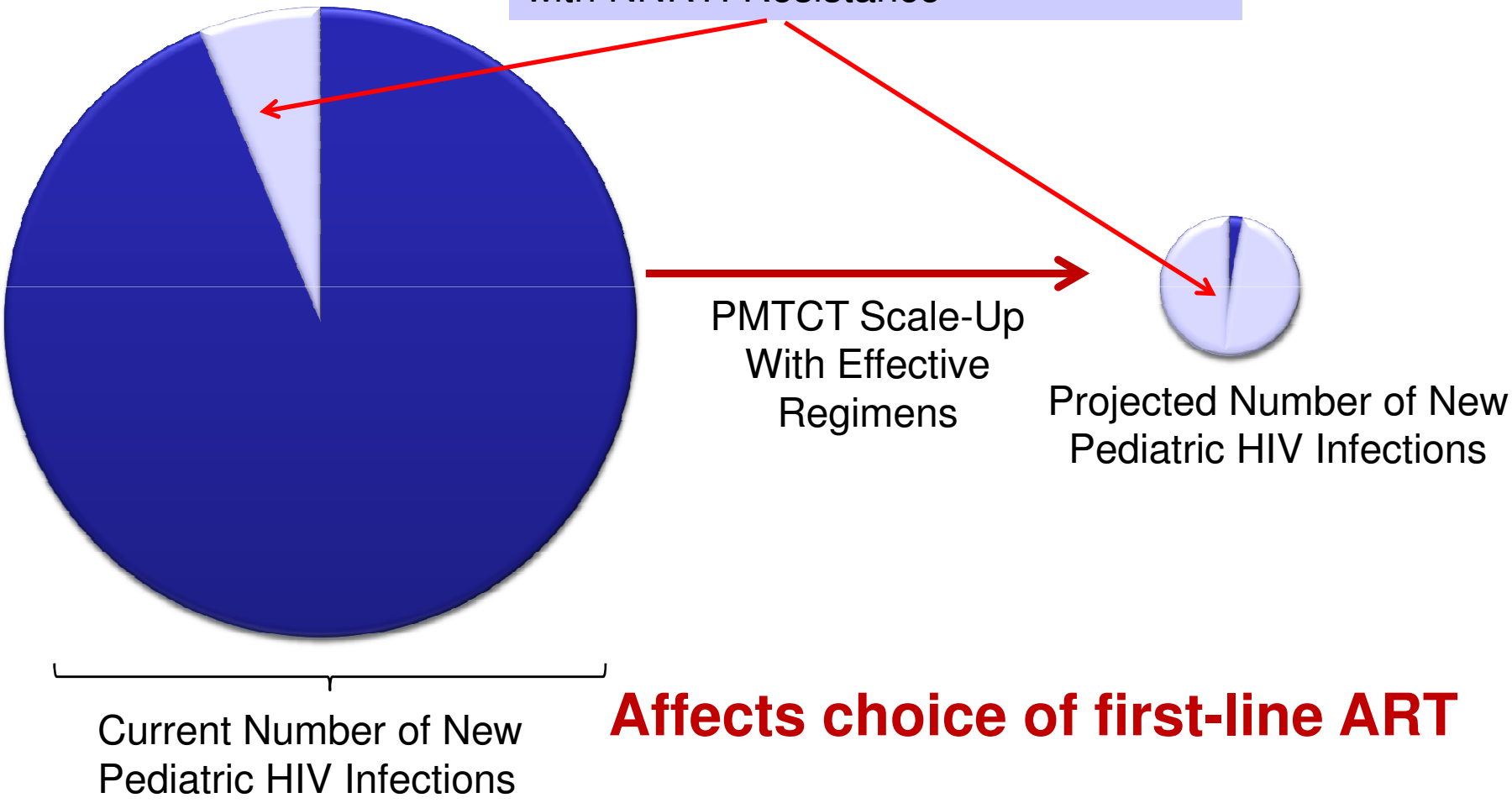
Patient group	Standard first-line regimen
INFANTS	
Infant or child <24 months not exposed to ARVs	NVP + 2 NRTI
Infant or child <24 months exposed to NNRTI	LPV/r + 2 NRTI
Infant or child <24 months with unknown ARV exposure	NVP + 2 NRTI
CHILDREN	
Children 24 months to 3 years	NVP + 2 NRTI
Children >3 years	NVP or EFV + 2 NRTI

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

AZT or d4T[a] + 3TC[b] + ABC

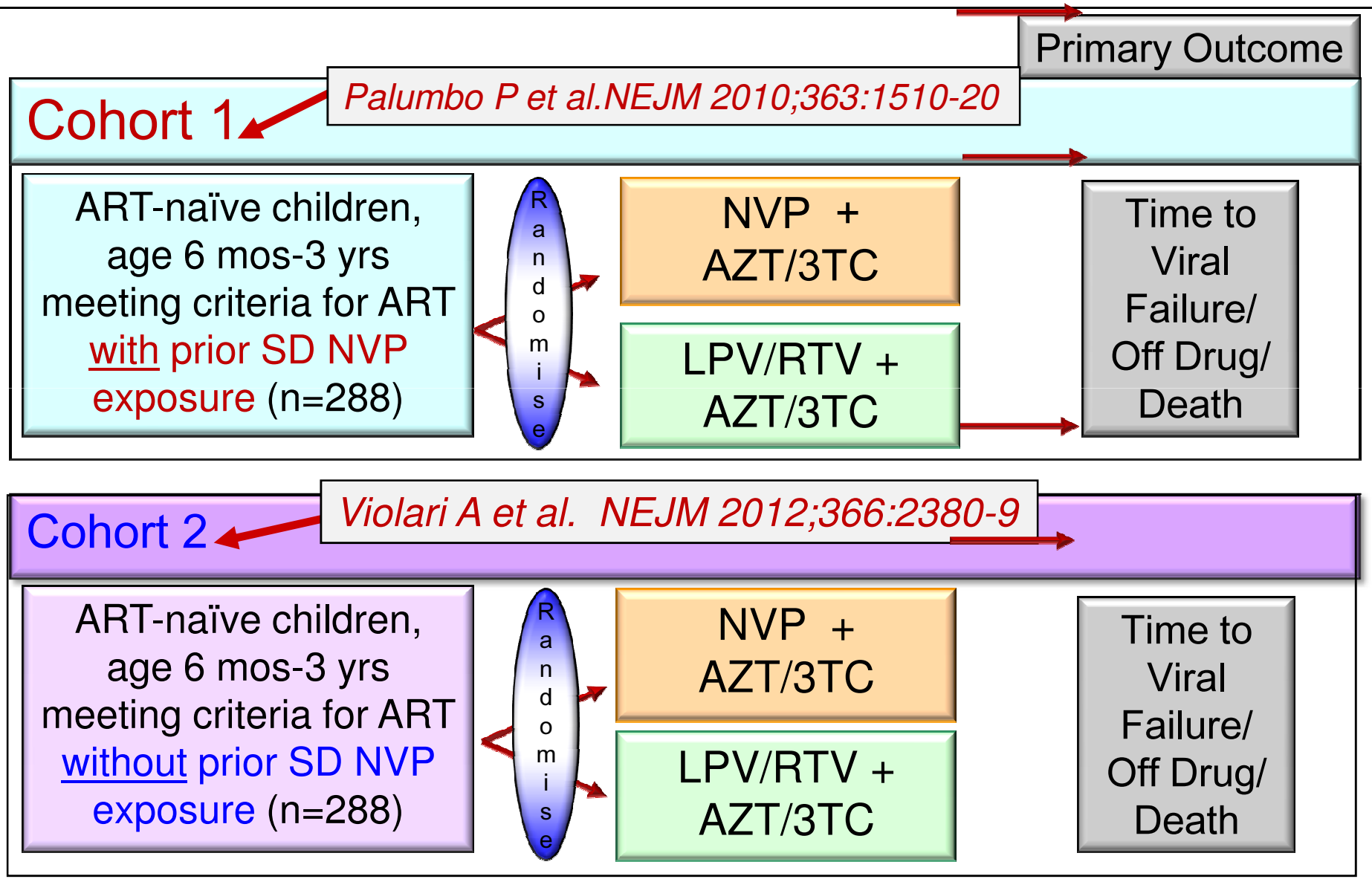
With Scale-Up of PMTCT, Smaller Number of Perinatally-Infected Infants but Greater Proportion with ARV Drug Resistance

Abrams E. 17th CROI, 2010



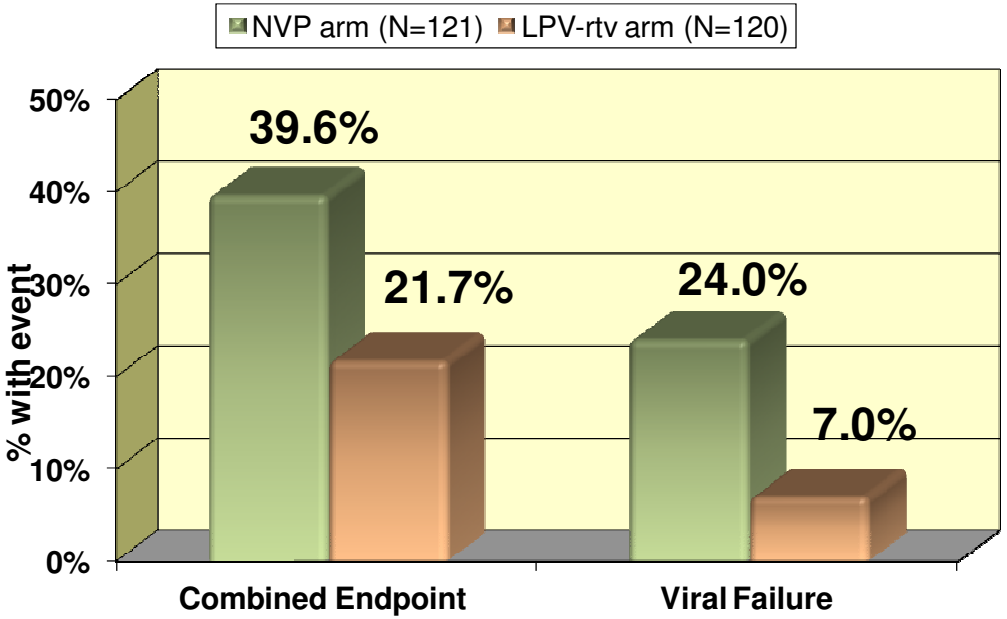
Affects choice of first-line ART

P1060: NVP vs LPV-r HAART in HIV-Infected Infants Under 3 Years

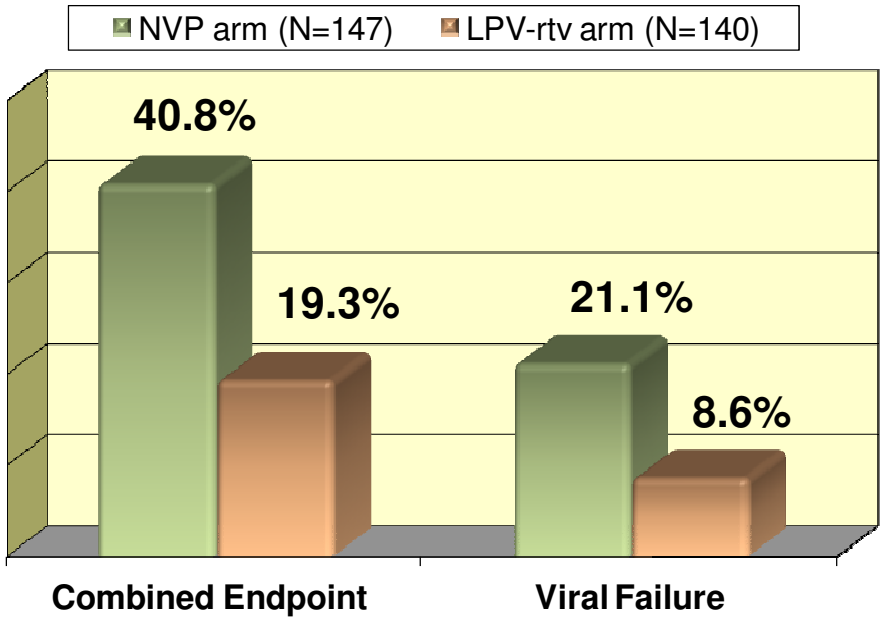


P1060 Results: Comparing Cohorts

Cohort 1: NVP-exposed



Cohort 2: No NVP Exposure



Combined endpoint= Viral Failure, Off Study Drug, or Death

- Similar rates of overall failure (combined endpoint) & viral failure in NVP-exposed AND -unexposed cohorts.
- Suggests PI (LPV/r) superior to NNRTI (NVP) for children <3 years old, regardless of past NNRTI exposure

NNRTI vs PI-Based ART in HIV-Infected Children and Malaria, Toro, Uganda

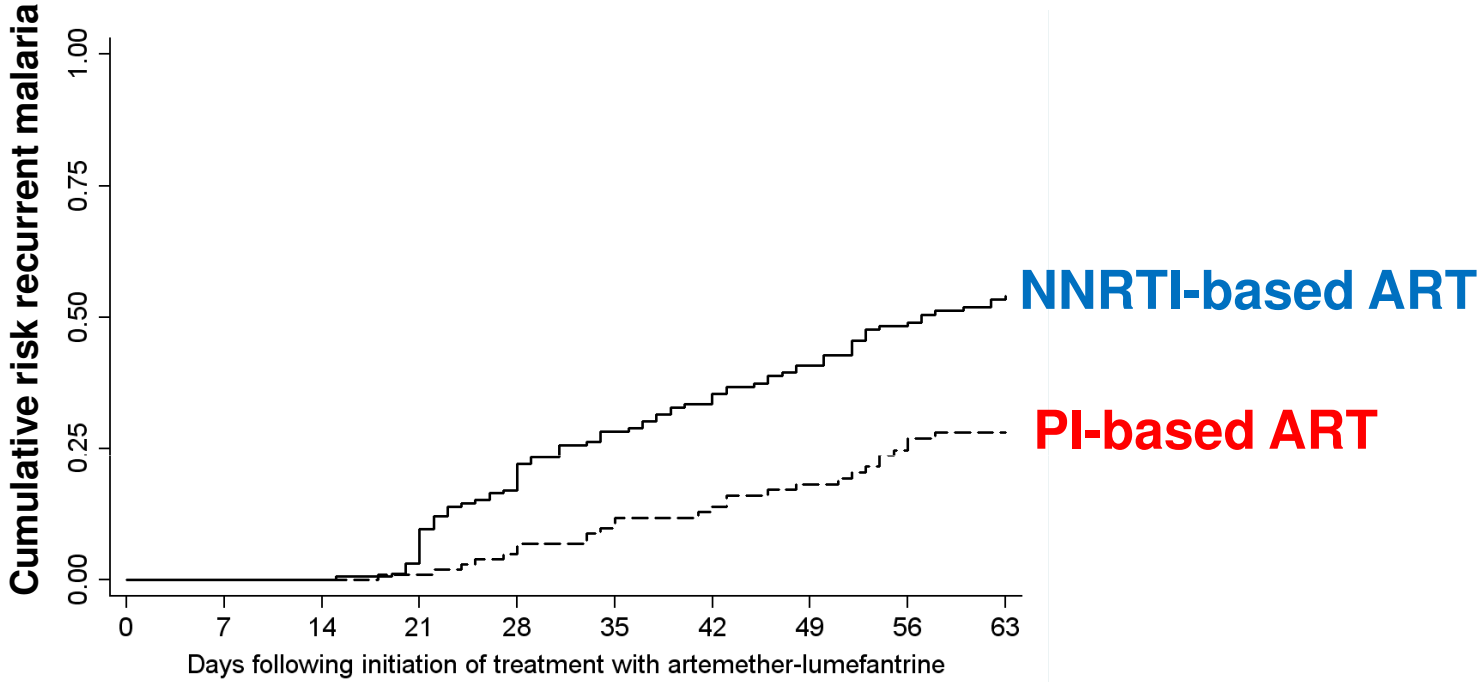
Achan J et al. NEJM 2012 Nov 29 in press

- 170 children aged 2 mo-5 yrs (median age ~3 yrs) randomized to initiate NNRTI vs LPV-based ART and followed for median 366 days; primary endpoint malaria incidence.

	NNRTI	LPV	HR	p value
Malaria incidence (episodes pt-yr)	2.25	1.32	0.59 (0.36-0.97) 41% decrease	0.04
63-day risk of recurrent malaria	54.2%	28.1%	0.41 (0.22-0.76) 59% decrease	0.004

Recurrent Malaria in HIV-Infected Children on LPV/rtv vs NNRTI-Based HAART, Toro, Uganda

Achan J et al. NEJM 2012 Nov 29 in press



- LPV associated with a 59% decrease in recurrent malaria after arthemther-lumefantrine (AL) rx (HR=0.41, 95% CI 0.22-0.76, p=0.004)
- RTV inhibits CYP 3A4 pathway involved in lumefantrine metabolism

	LPV/r –based ART	NNRTI-based ART	P value
Median day 7 lumefantrine level ng/ml (IQR)	926 (473-1910)	200 (108-510)	<0.0001

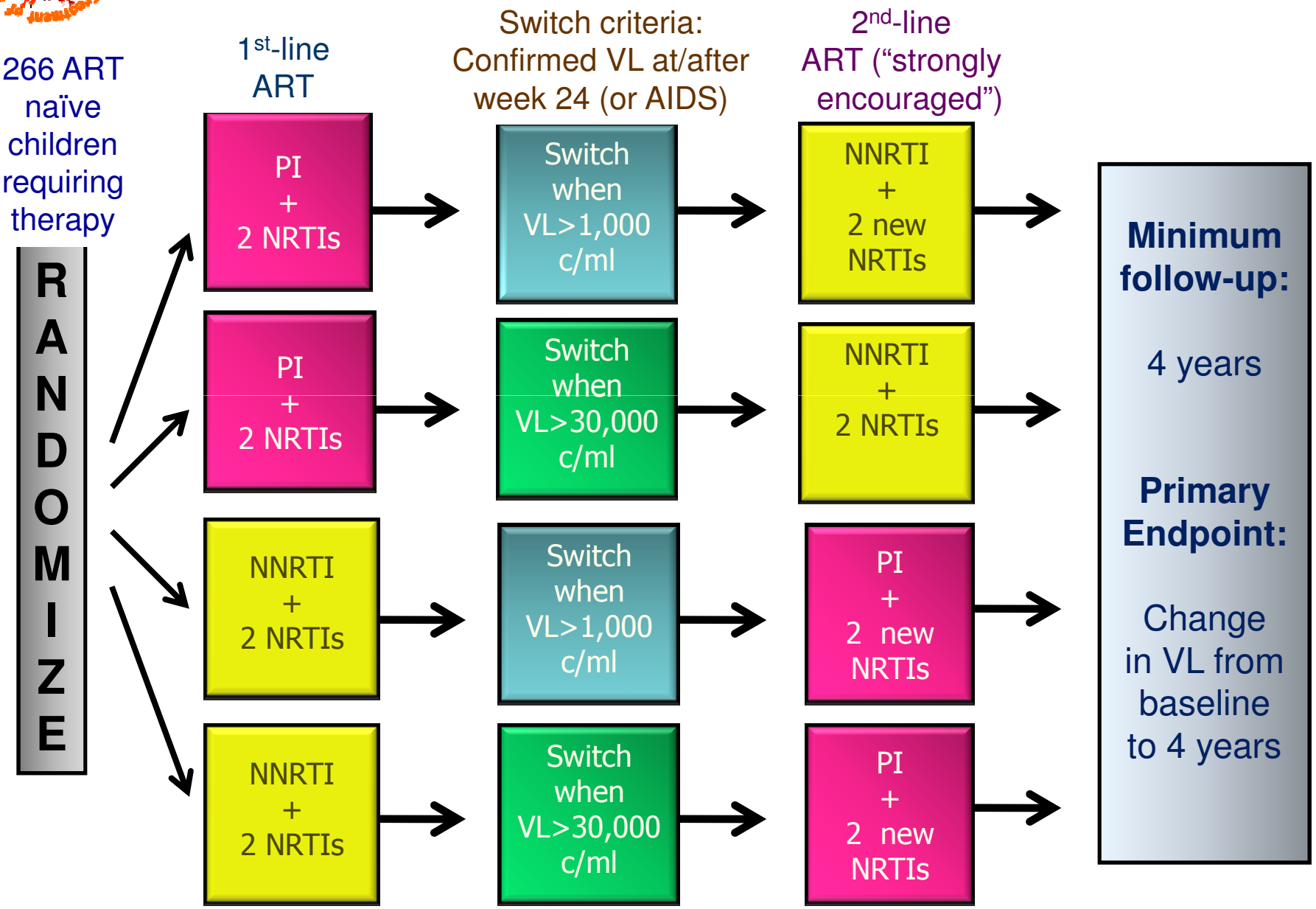
NNRTI vs PI as Initial Therapy in Older Children: A Different Trial with a Different Story to Tell….

PENPACT-1/ PACTG 390

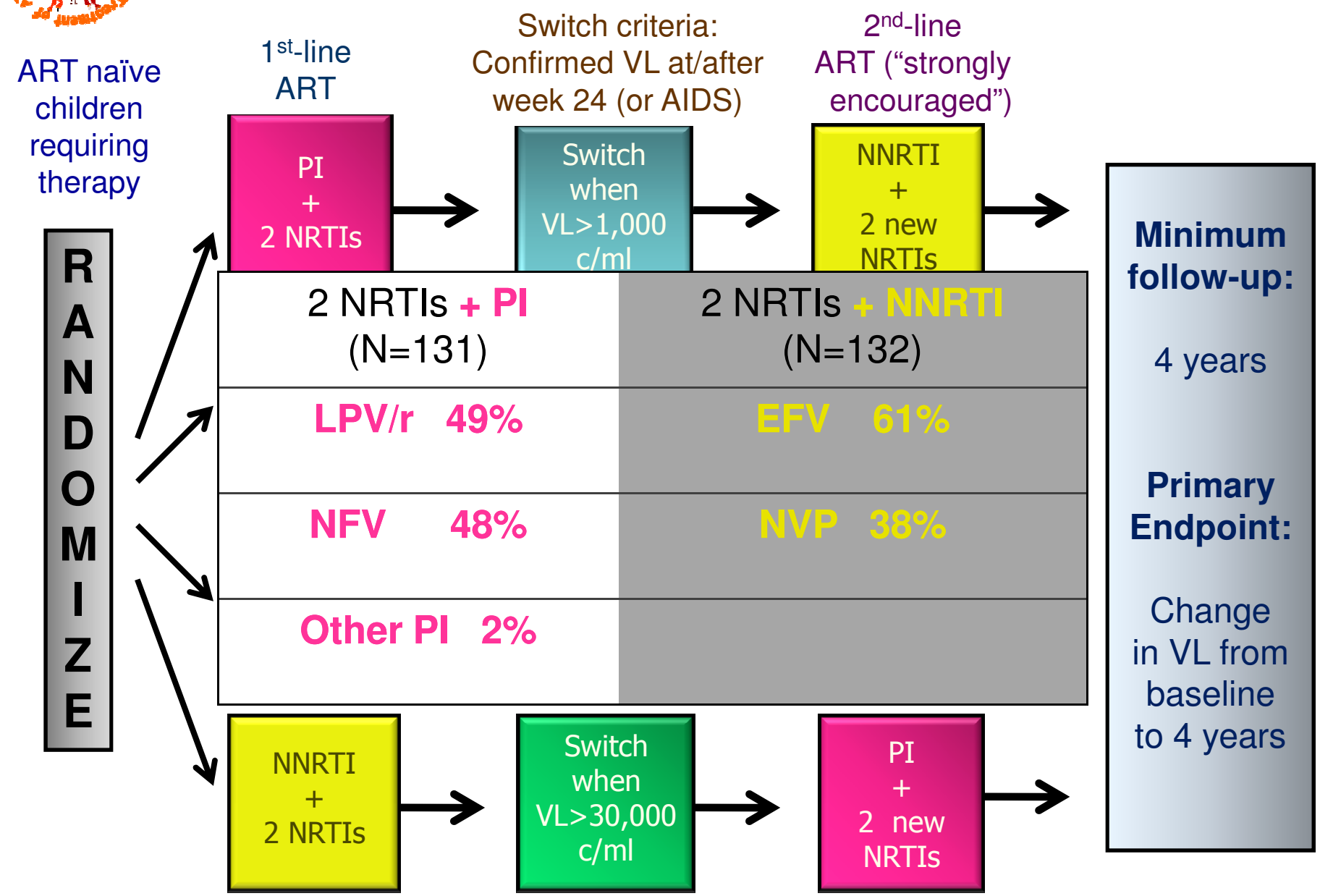
(Europe & Americas)

- Initial Therapy
- VL for switching

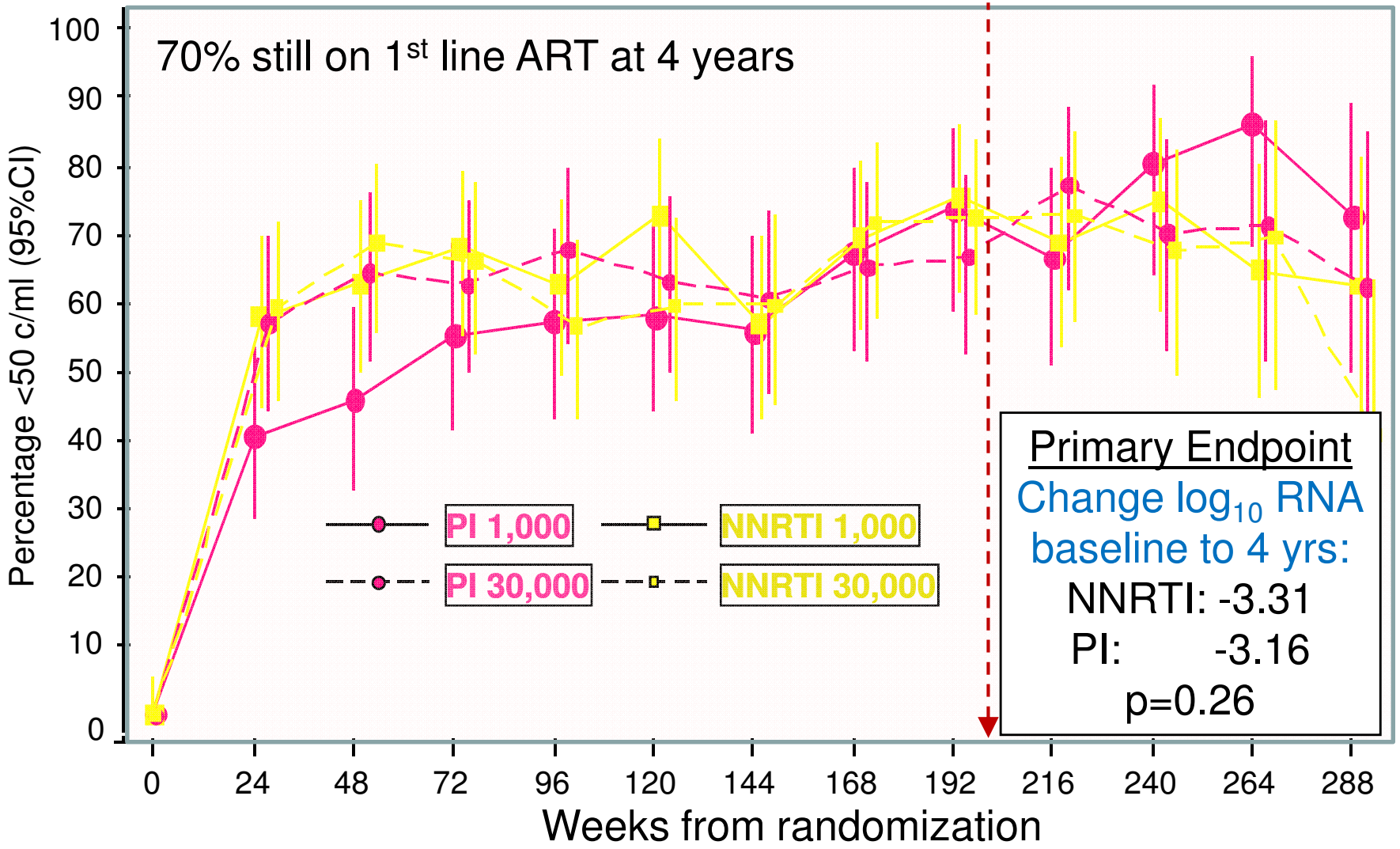
PENPACT-1/ PACTG 390



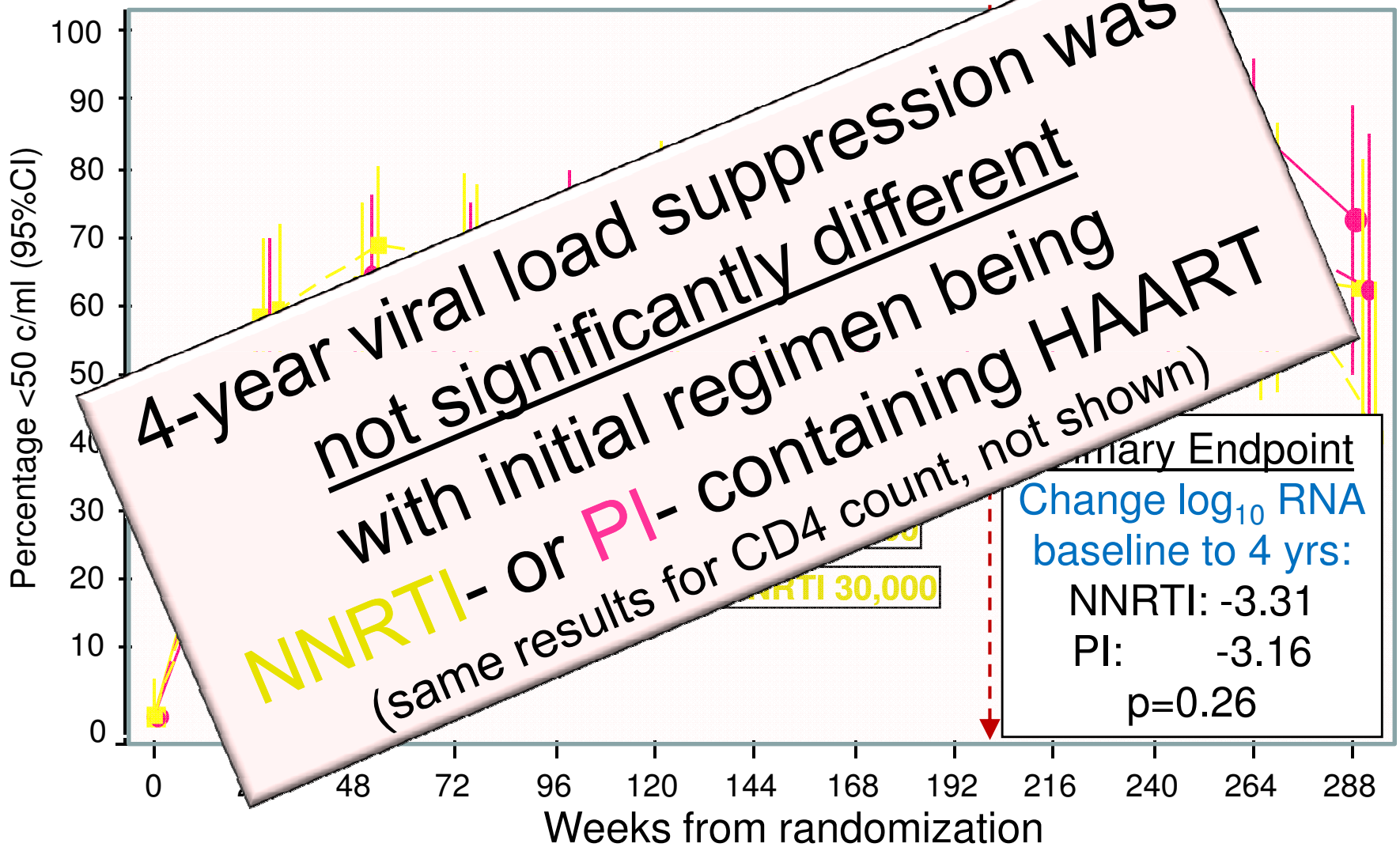
PENPACT-1/ PACTG 390



PENPACT-1/PACTG 390: Proportion with HIV-1 RNA <50 c/ml



PENPACT-1/PACTG 390: Proportion with HIV-1 RNA <50 c/ml



4-year viral load suppression was not significantly different with initial regimen being NNRTI- or PI- containing HAART (same results for CD4 count, not shown)

P1060 #2 (not NVP exposed) vs. PENPACT-1: Conflicting Results for PI vs NNRTI-based HAART

Characteristic	P1060 Cohort 2	PENPACT/PACTG 390
Median Age (Range)	**1.7y** (0.5-3y)	**6.5 y** (0.1-17.8y) 26% ≤3 yo
Setting	**Africa**, India	**Euro,** US, Brazil, Arg. Carib.
NNRTI	100% NVP	38% NVP; **61% EFV**
PI	100% LPVr	49% LPVr; **48% NFV**
Previous NVP exp	None	2%
Subtype B	None	41%

- Preferred initial regimens for younger (≤ 3 yr old) and older (> 3 yr old) children may be different
- May get different results depending on which drug(s) used in NNRTI or PI class
- Differences by host and virus genetics?

Other Strategies?

Would NVP work better once virologic suppression is achieved on a PI regimen?

JAMA The Journal of the American Medical Association

Reuse of Nevirapine in Exposed HIV-Infected Children After Protease Inhibitor–Based Viral Suppression

A Randomized Controlled Trial

Ashraf Coovadia, MBChB
Elaine J. Abrams, MD
Renate Stehlau, MBChB
Tammy Meyers, MBChB
Leigh Martens, MBChB
Gayle Sherman, MBChB, PhD
Gillian Hunt, PhD
Chih-Chi Hu, MS
Wei-Yann Tsai, PhD
Lynn Morris, PhD
Louise Kuhn, PhD

JAMA, September 8, 2010—Vol 304, No. 10 (Reprinted)

version of mother-to-child HIV transmission. However, there are limitations of continuing PI-based therapy indefinitely and reuse of nevirapine has many advantages.

Objective To test whether nevirapine-exposed infants who initially achieve viral suppression with PI-based therapy can maintain viral suppression when switched to nevirapine-based therapy.

Design, Setting, and Patients Randomized trial conducted between April 2005 and May 2009 at a hospital in Johannesburg, South Africa, among 195 children who achieved viral suppression less than 400 copies/mL for 3 or more months from a cohort of 323 nevirapine-exposed children who initiated PI-based therapy before 24 months of age.

Interventions Control group children continued to receive ritonavir-boosted lopinavir, stavudine, and lamivudine (n=99). Switch group children substituted nevirapine for ritonavir-boosted lopinavir (n=96).

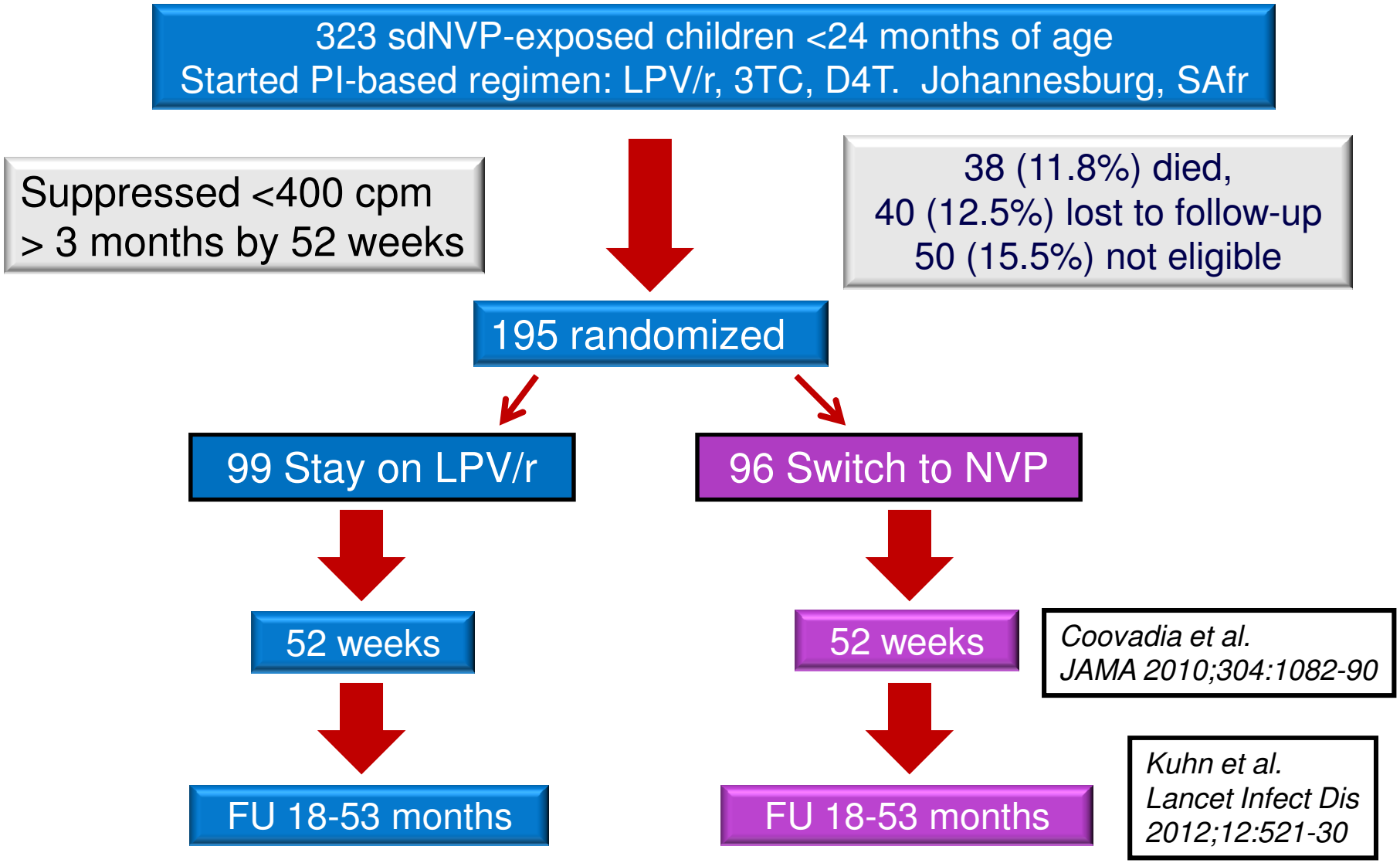
THE LANCET Infectious Diseases
Volume 12, Issue 7, July 2012, Pages 521–530

Articles

Switching children previously exposed to nevirapine to nevirapine-based treatment after initial suppression with a protease-inhibitor-based regimen: long-term follow-up of a randomised, open-label trial

Prof Louise Kuhn, PhD[a], Prof Ashraf Coovadia, FCP [Paeds][d], Renate Strehlau, MBBCh[d], Leigh Martens, MBBCh[d], Chih-Chi Hu, MS[b], Tammy Meyers, MD[e], Gayle Sherman, PhD[f,g], Gillian Hunt, PhD[h], Deborah Persaud, MD[i], Prof Lynn Morris, PhD[h], Prof Wei-Yann Tsai, PhD[b], Prof Elaine J Abrams, MD[c]

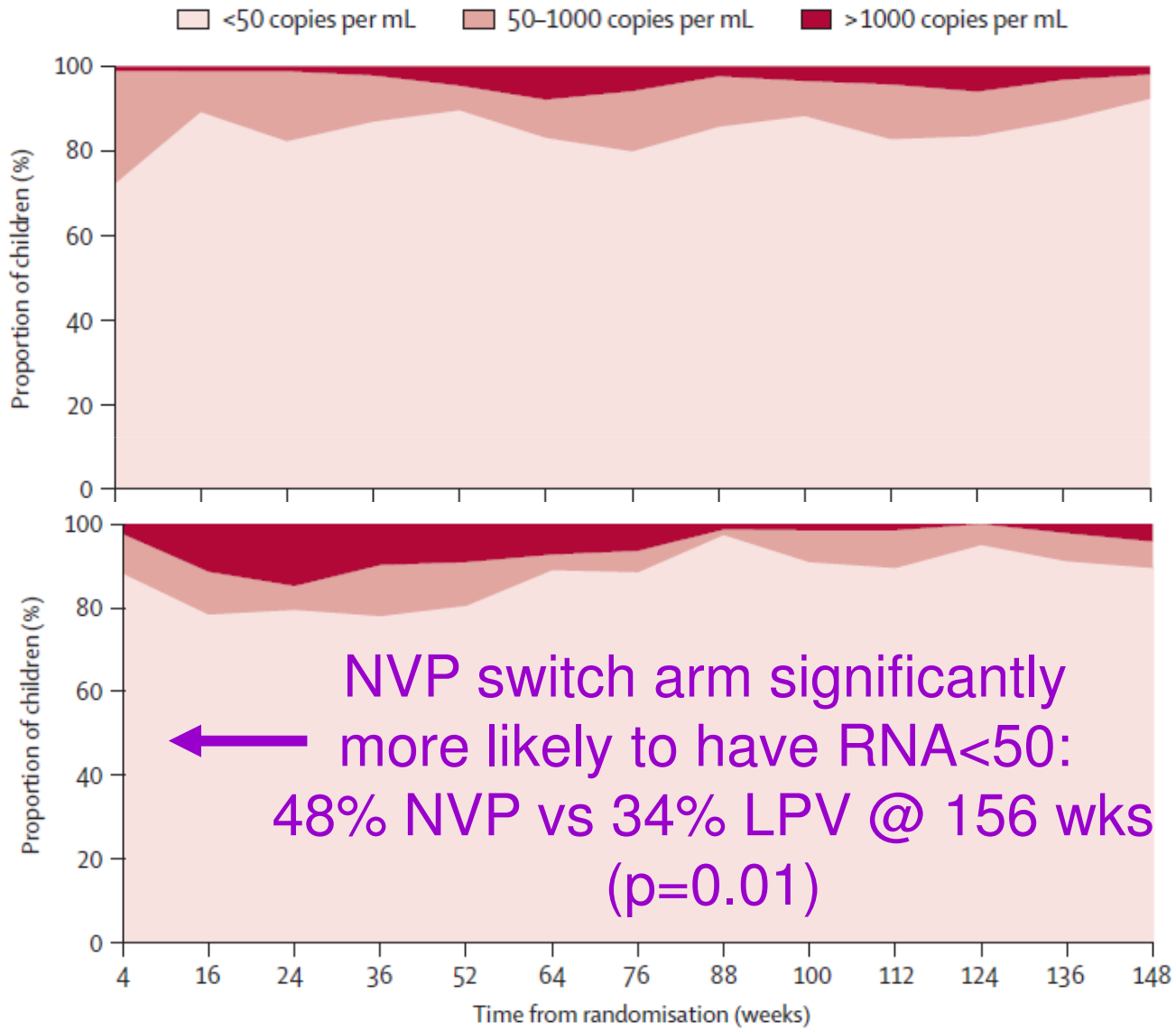
NEVEREST STUDY



Proportions of Children with RNA <50, 51-1000 or >1,000 c/mL at Each Visit through 148 Weeks

LPV

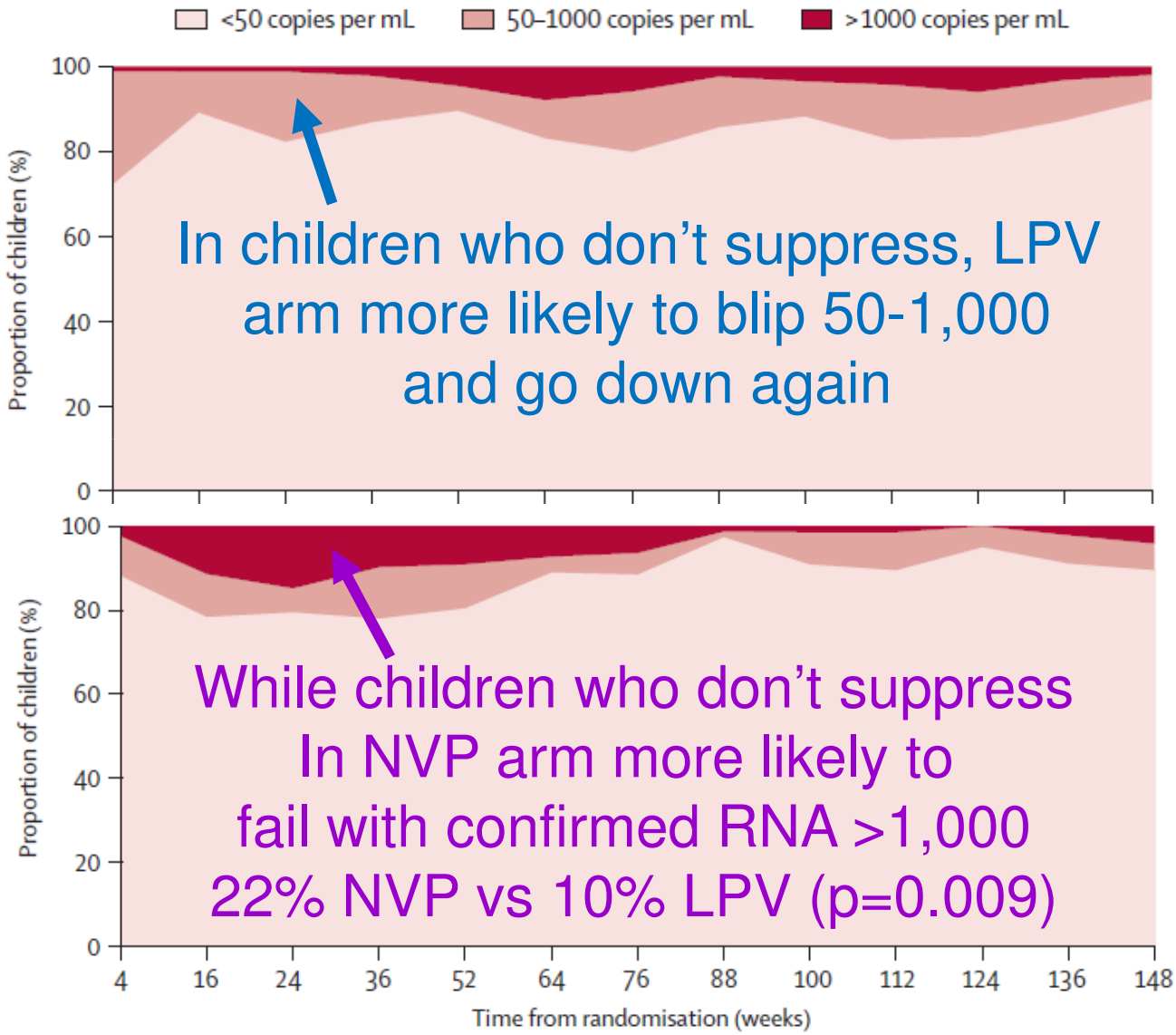
NVP Switch



Proportions of Children with RNA <50, 51-1000 or >1,000 c/mL at Each Visit through 148 Weeks

LPV

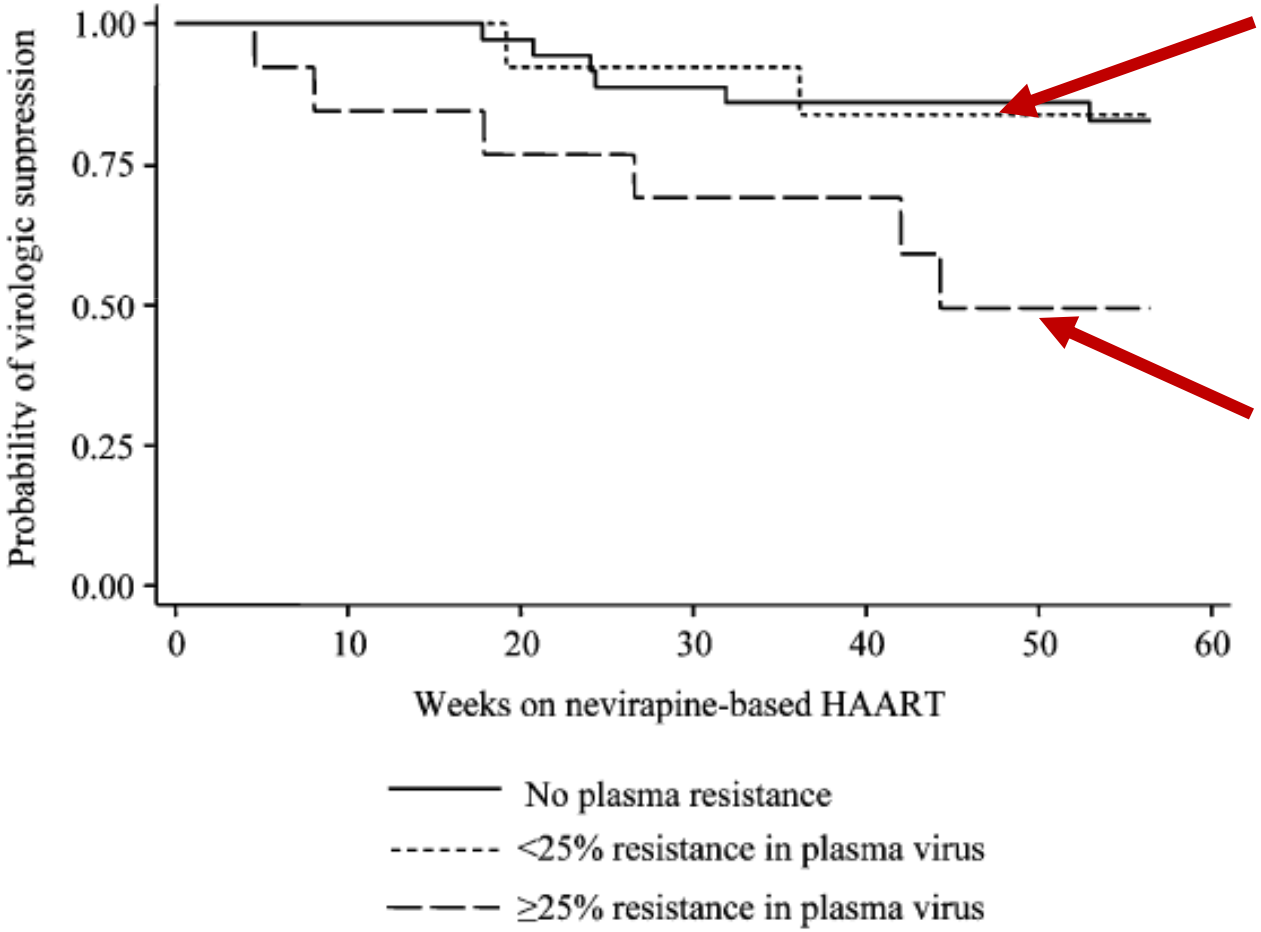
NVP Switch



Viral Failure in Switch Arm Primarily Secondary to Pre-ART Drug Resistance Frequency ≥25%

Moorthy A et al. Clin Inf Dis 2011;52:514-21

Failure NVP switch with no resistance 14% vs LPV 10% (p=0.34)



- Low frequency resistance not associated with failure
- 3.5-fold higher risk failure in children with ≥25% resistant virus

Other Strategies?

Induction with 4 drugs?

Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants

Andrew Prendergast[a], Wendy Mphatswe[b], Gareth Tudor-Williams[c], Mpho Rakgotho[d], Visva Pillay[d], Christina Thobakgale[b], Noel McCarthy[a], Lynn Morris[d], Bruce D. Walker[b,e,f] and Philip Goulder[a,b,e]

AIDS 2008, **22**:1333–1343

Early antiretroviral therapy in HIV-1-infected infants, 1996-2008: treatment response and duration of first-line regimens

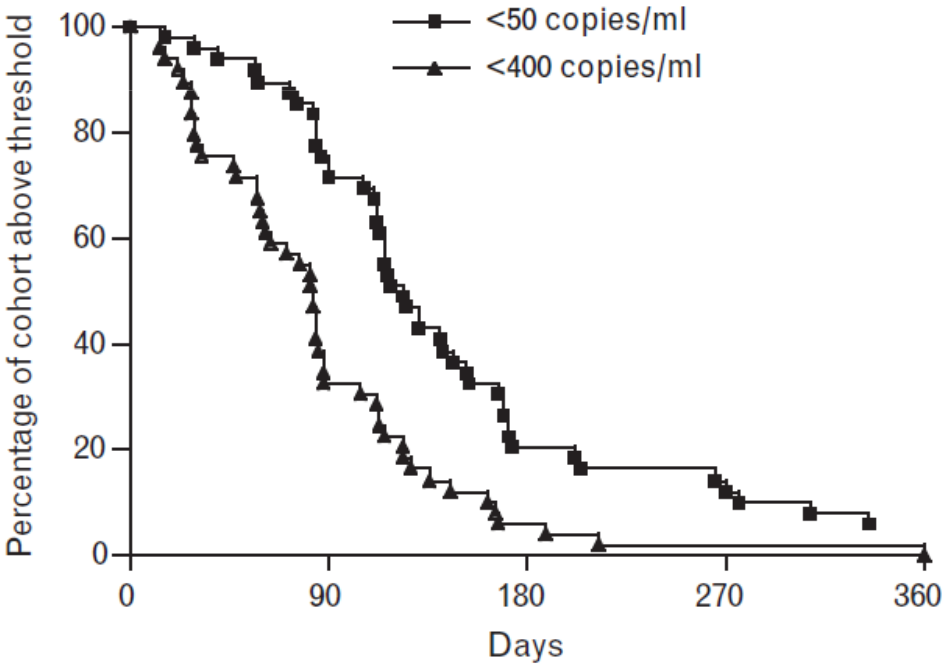
The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord

AIDS
Issue: Volume 25(18), 28 November 2011, p 2279-2287
Copyright: © 2011 Lippincott Williams & Wilkins, Inc.
Publication Type: [CLINICAL SCIENCE]
DOI: 10.1097/QAD.0b013e32834d614c
ISSN: 0269-9370
Accession: 00002030-201111280-00010
Keywords: antiretroviral therapy, drug switching, Europe, infant

Early Viral Suppression with 3-Class ART in HIV-Infected Infants Exposed to SdNVP

Prendergast A et al. AIDS 2008;22:1333-43

- In Durban, South Africa, infants exposed to sdNVP received AZT/3TC/NFV/NVP at median age 42 days.
- NNRTI resistance mutations were found in 39%.



- Of 49 infants on ART, all had RNA <400 and 94% <50 within a year of starting ART
- No significant difference in time to undetectable in infants with and without resistance

Can Early ART Be Safely Interrupted?

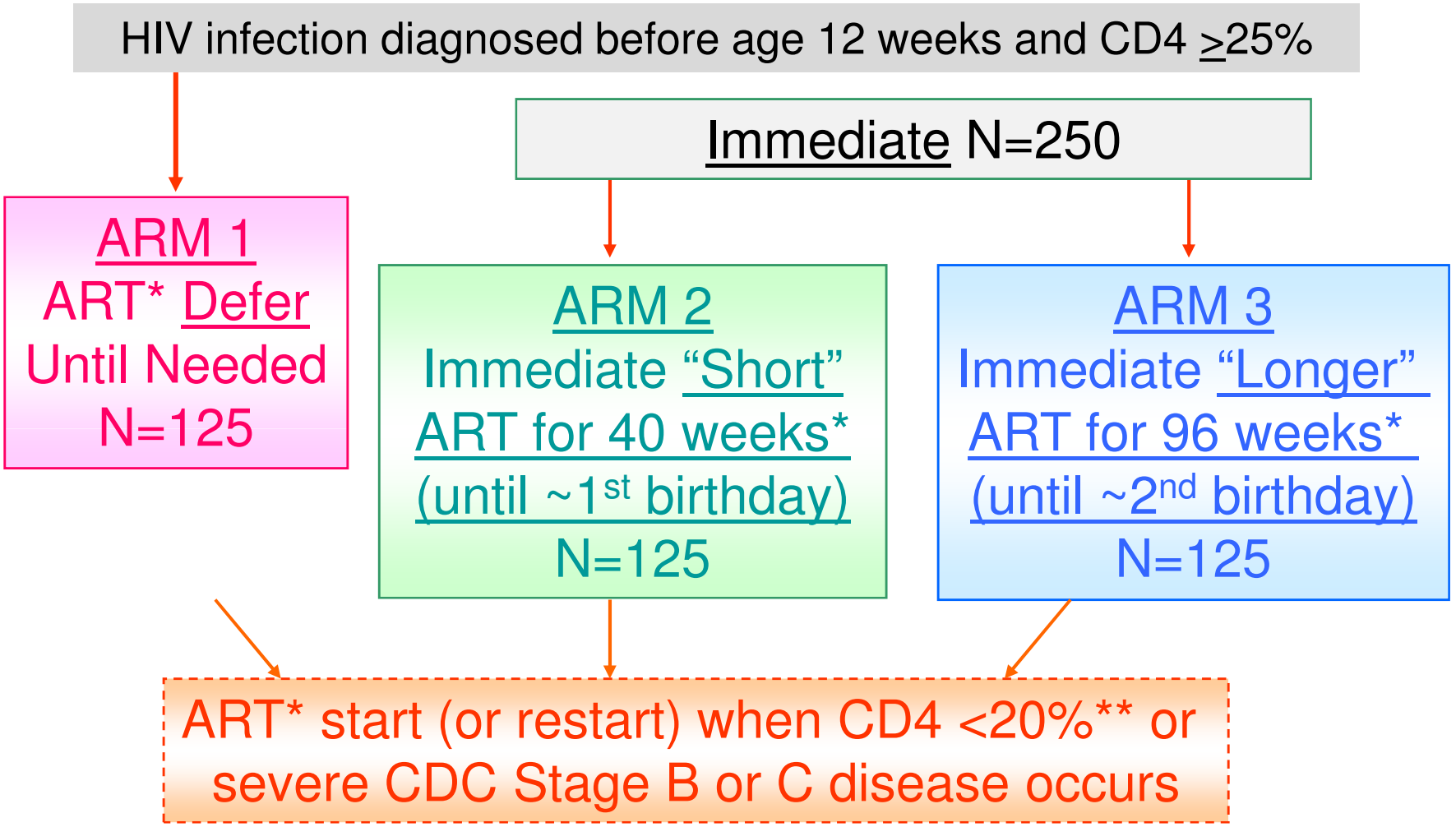
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Antiretroviral Therapy and Mortality among HIV-Infected Infants

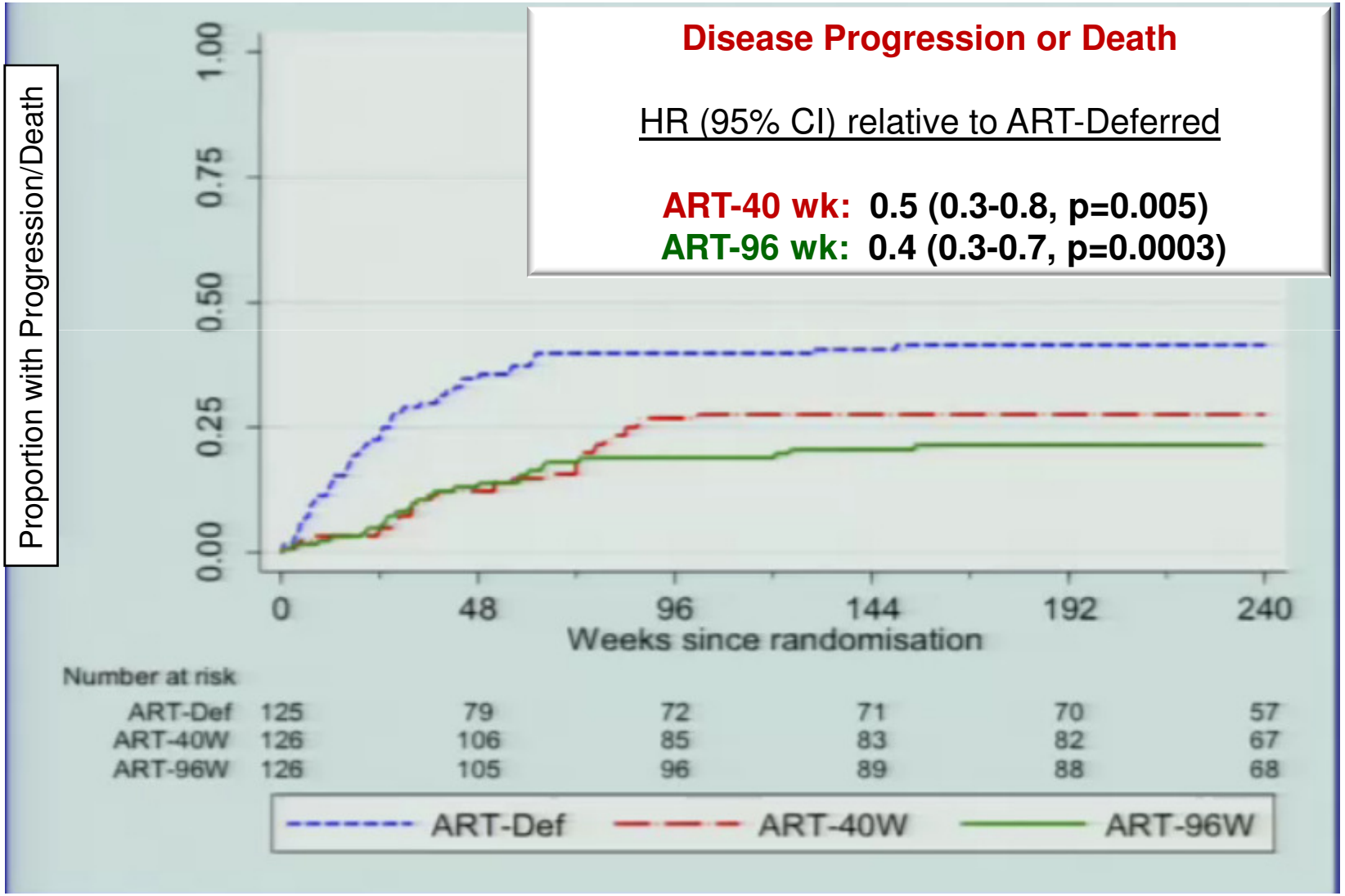
Avy Violari, F.C.Paed., Mark F. Cotton, M.Med., Ph.D., Diana M. Gibb, M.D., Abdel G. Babiker, Ph.D., Jan Steyn, M.Sc., Shabir A. Madhi, F.C.Paed., Ph.D., Patrick Jean-Philippe, M.D., and James A. McIntyre, F.R.C.O.G., for the CHER Study Team*

Children with HIV Early AntiRetroviral Therapy (CHER) Study



*ART = AZT/3TC/LPV/r

CHER: Disease Progression (Severe B or C) or Death
ART-Deferred vs ART-40 wk vs ART-96 wk
Cotton M et al. 19th CROI, Seattle, WA, March 2012 (Abs 28LB)



CHER: Treatment Interruption Phase

Cotton M 19th CROI, Seattle, 2012

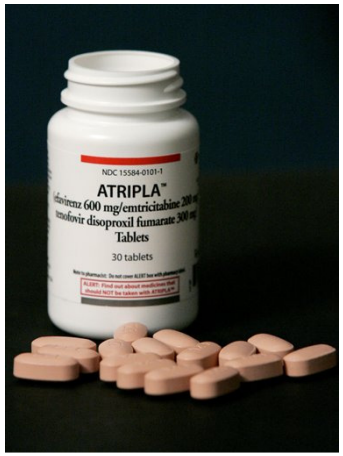
- Early ART until 1st or 2nd birthday followed by interruption compared to deferred ART appears safe in children with regular CD4 and clinical monitoring and results in less ART exposure (potential cost-saving).
- Early ART for 2 years compared to 1 year results in longer subsequent interruption and rrend toward fewer clinical events.
- Further analysis needed to evaluate viral suppression, resistance, immune response and neuro-developmental consequences after ART restart.

You Can't Treat Pediatric HIV Without Drugs!
Critical Need for New Drug Formulations in Children

Pediatric Antiretroviral Drugs

What is Available and Needed

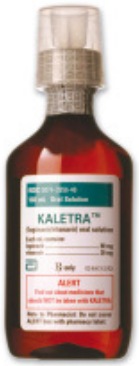
What is Available for Adults



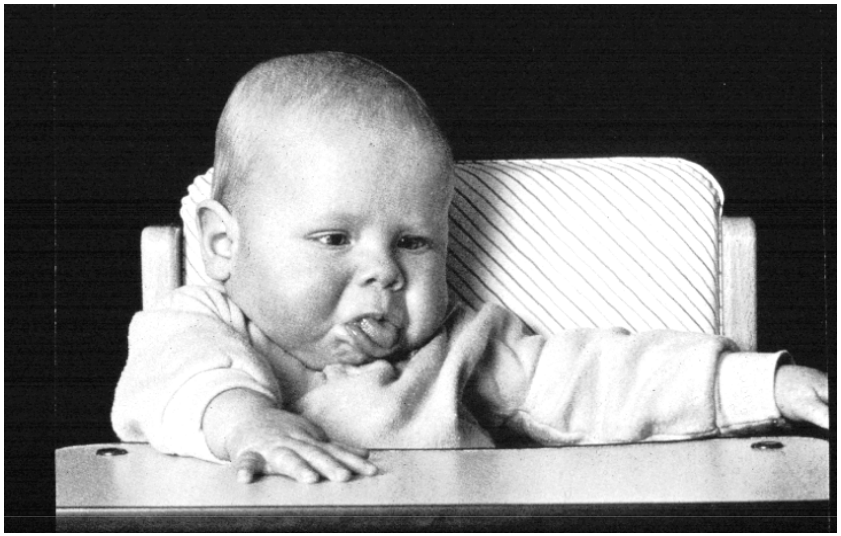
FDCs that allow one pill once daily

4-drugs in one – once daily

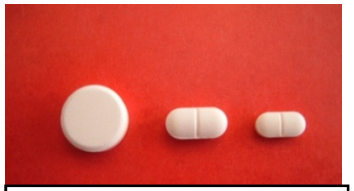
What is Available in Children



80 mg/20 mg/mL Kaletra oral solution [lopinavir/ritonavir]



What We Need for ARVs in Children



FDCs that allow one pill daily

Fentanyl lollipop

Triaminic orange flavor chewables

Dextromethorphan dissolvable strip

Triaminic patch

Sachet

Summary

- Resource-rich countries most children are receiving ART with an individualized intensive monitoring approach.
- In resource-limited countries, progression is more rapid and while children respond well to ART, therapy started at older age and low CD4, resulting in higher mortality on ART than in rich countries.
- Initiation of ART in early infancy is optimal but complicated by drug resistance from exposure to PMTCT drugs.
- While NNRTI-based ART seems effective in older children, PI-based ART appears optimal for infants.
- Use of switch or induction strategies requires further study.
- More drug choices and formulations needed in children!

Thanks For Your Attention

Special thanks to:
George Siberry