

Paediatric HIV

Addressing the ART needs of under-3 HIV infected children

Durban September 2011

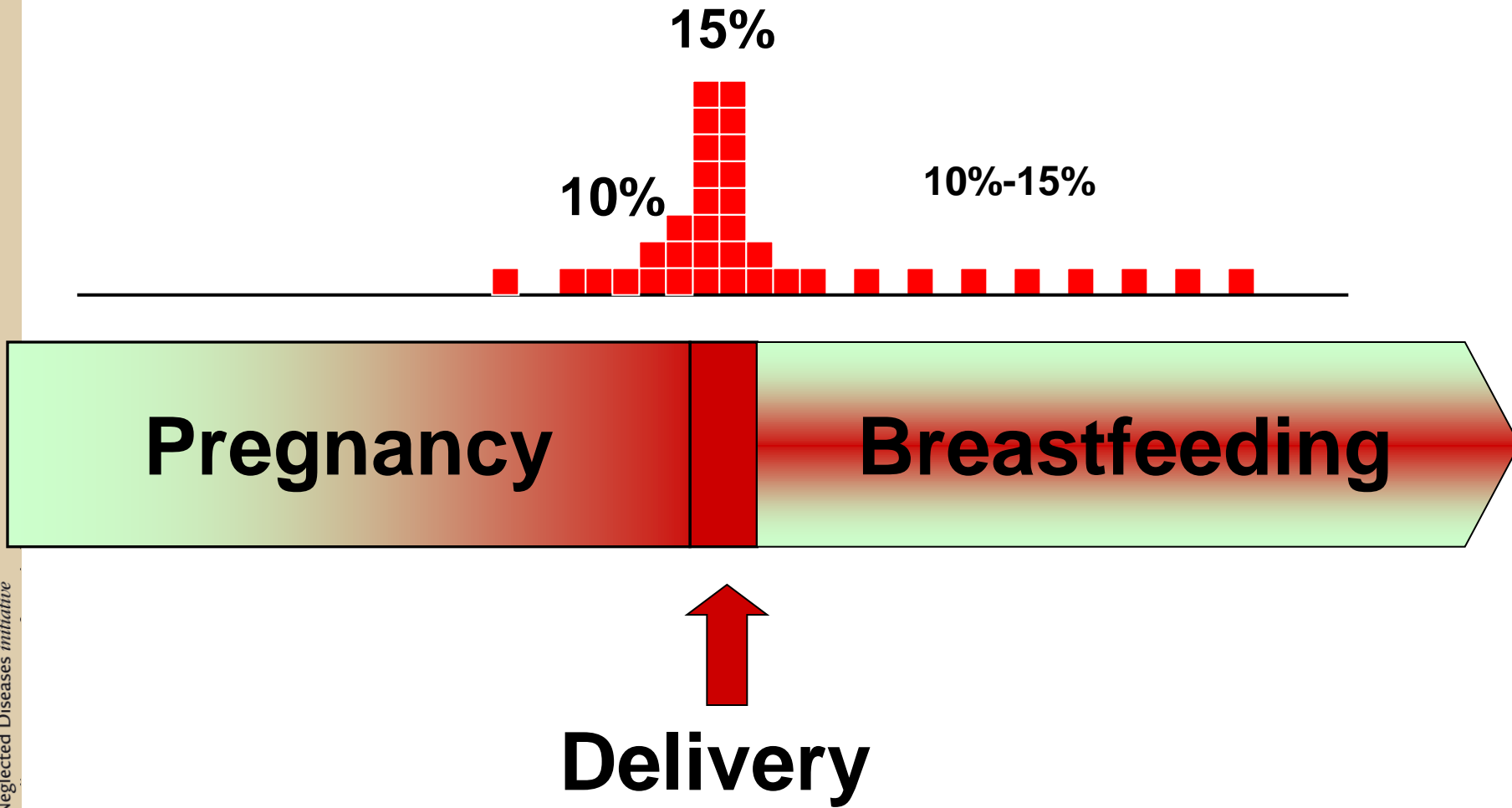
Marc Lallemand

mlallemand@dndi.org

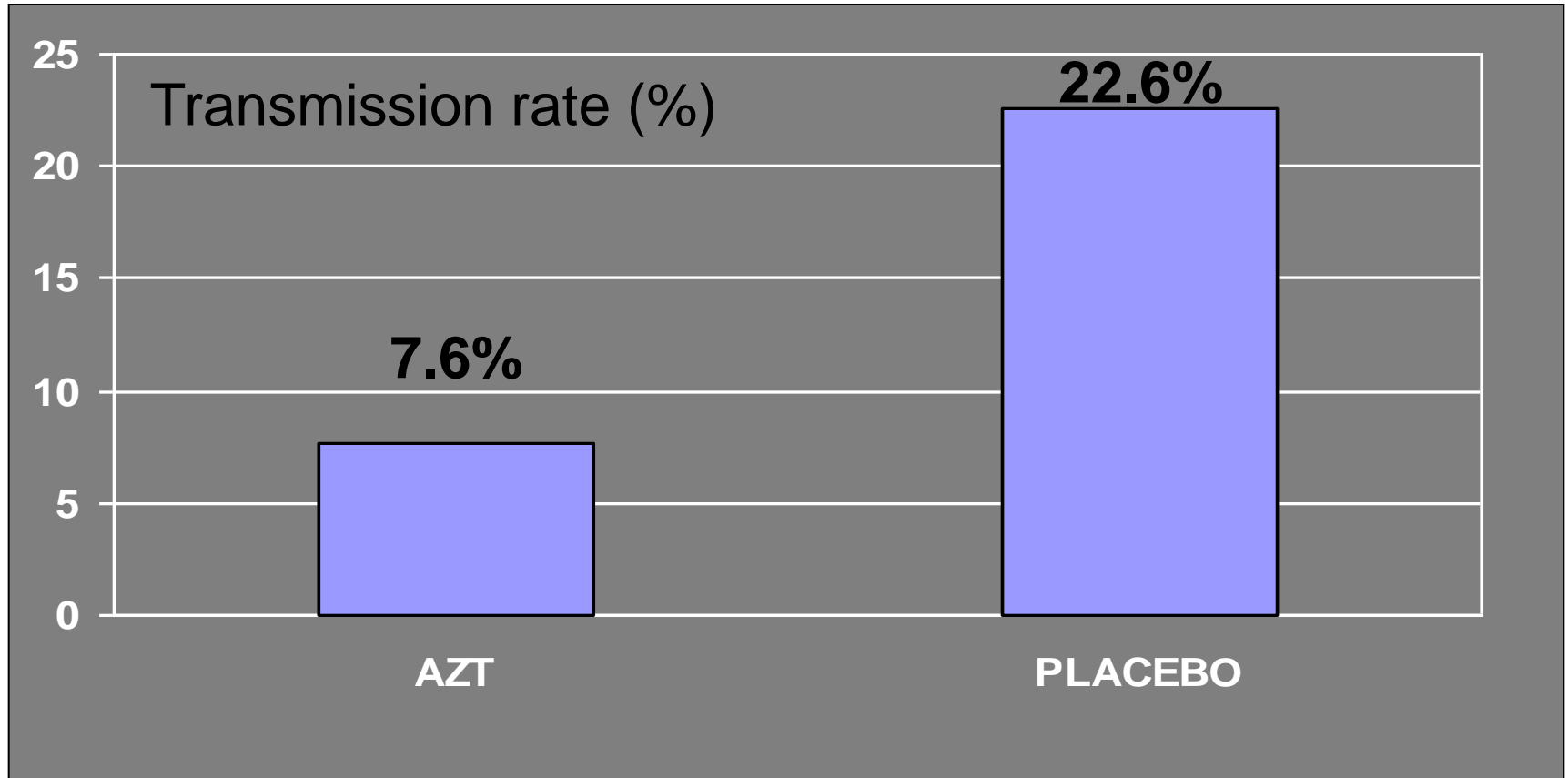
DNDi

Drugs for Neglected Diseases *initiative*

Timing of mother-to-child transmission



Pediatric AIDS Clinical Trial Group Protocol 076 (PACTG 076/ANRS) (Non breast-feeding mothers)



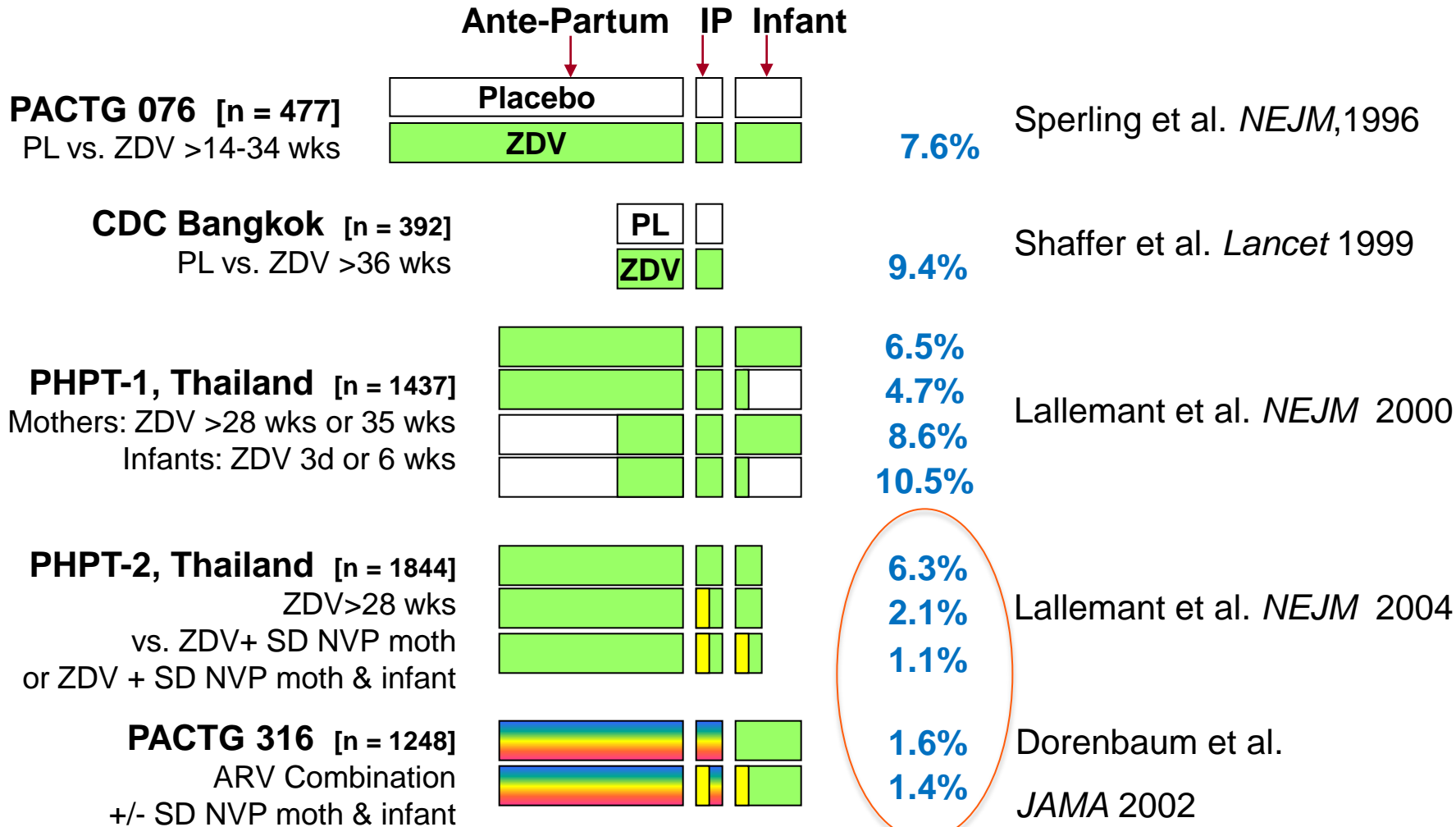
from 14 to 34 weeks gestation
until delivery; IV infusion during
labor; Infants for 6 weeks

Sperling RS N Engl J Med, 1996;335:1173-1180

Fifteen years of intense clinical research

- PACTG076/ANRS results were followed by 15 years of uninterrupted clinical research
 - ARV trials in pregnancy and/or at delivery in non breast feeding women
 - ARV trials in pregnancy and/or at delivery in breast feeding women
 - ARV trials for the whole duration of (exclusive) breastfeeding
- Perinatal HIV can virtually be eliminated

Randomized trials: Non-breastfeeding mothers

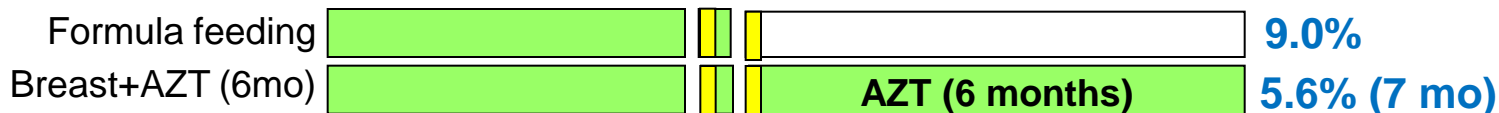


ARV randomized trials: Breastfeeding mothers

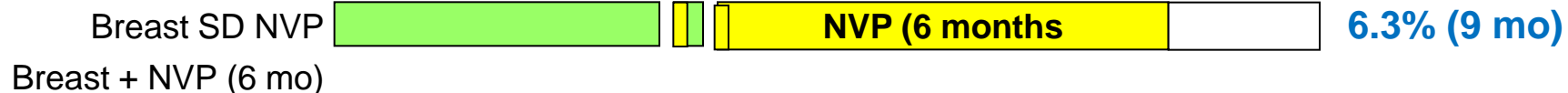
	Ante-Partum	IP Inf	Post-Partum		
CDC, Abidjan [n = 280] PL vs. ZDV>36 wks					Wiktor et al. <i>Lancet</i> 1999 16.5% (12 wks)
Ditrame, Abidjan/Bobo [n = 400] PL vs. ZDV>36-38 wks					Dabis et al. <i>Lancet</i> 1999 18.0% (24 wks)
PETRA : ZDV+3TC [n = 1797] AP >36 wks +IP+Infant+PP vs. IP+Infant+PP vs. IP vs. PL					Petra Study Team. <i>Lancet</i> 2002 5.7% 8.9% 14.2%
HIVNET 012 [n = 626] ZDV IP+Infants 7d vs. SD NVP Moth & Infant					Guay et al. <i>Lancet</i> 1999 25.1% 13.1% (14-16 wks)
SAINT [n = 1391] ZDV+3TC vs. SD NVP Moth & Infant + Post-partum					Moodley et al. <i>JID</i> 2003 9.3% 12.3% (8 wks)
MASHI, Botswana [n = 1179] ZDV>34 wks vs. ZDV+ SD NVP infant or ZDV + SD NVP moth & infant					Shapiro et al. CROI 2005 6.2% 3.7% 4.3-5.3% (4 wks)

Trials using ARVs during breastfeeding

Dream¹ [n = 1,200]



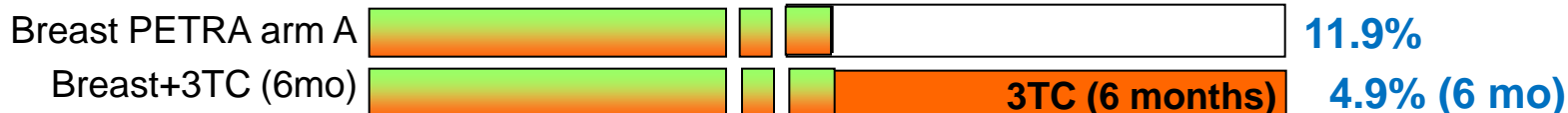
MITRA+² [n = 3,016]



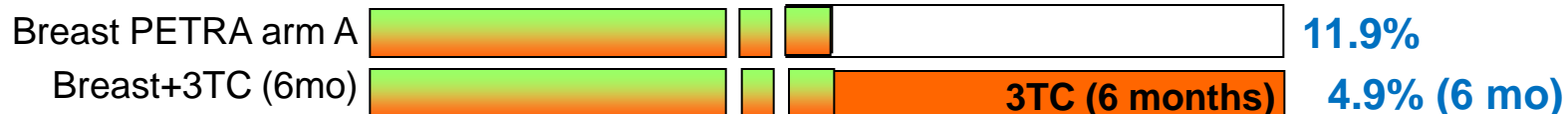
AMATA³ [n = 2,024]



KIBS⁴ [n = 477]



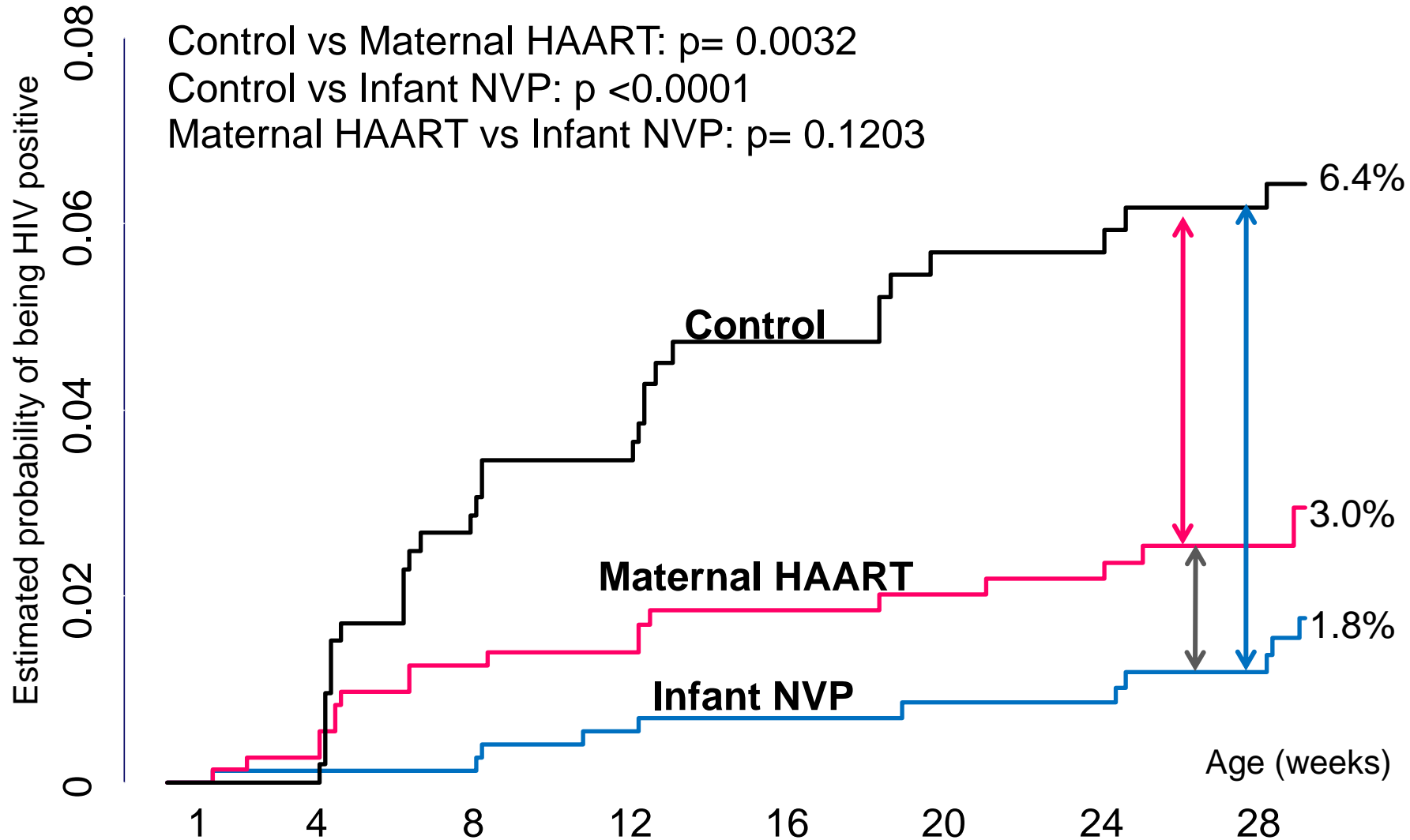
MTCT+⁵ [n = 477]



1. Thior I, et al. JAMA 2006
2. Kumwenda NI, et al. NEJM 2008
3. SWEN Study team, Lancet 2008
4. Kilewo C, et al. J AIDS 2008

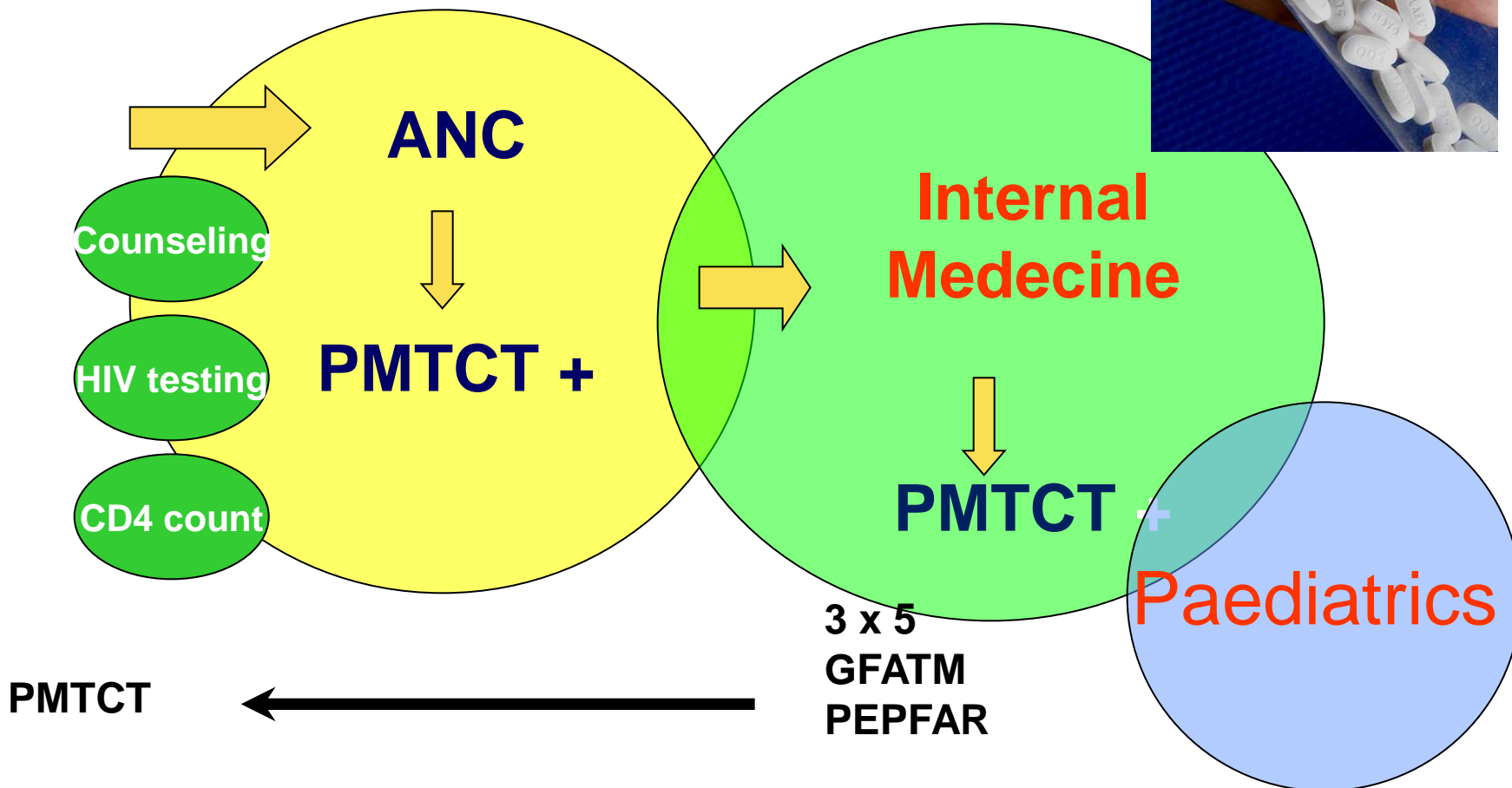
BAN: Probability of HIV Infection by Week 28 in Infants Uninfected at Birth

Chasela C et al. IAS, Capetown, South Africa, July 2009 Abs. WELBC103



From PMTCT to HAART to PMTCT and back ?

HIV+ Pregnant Women/Partners



2010 WHO recommendations

< 350 ASAP no stop



OR



> 350 from 14 weeks on ...

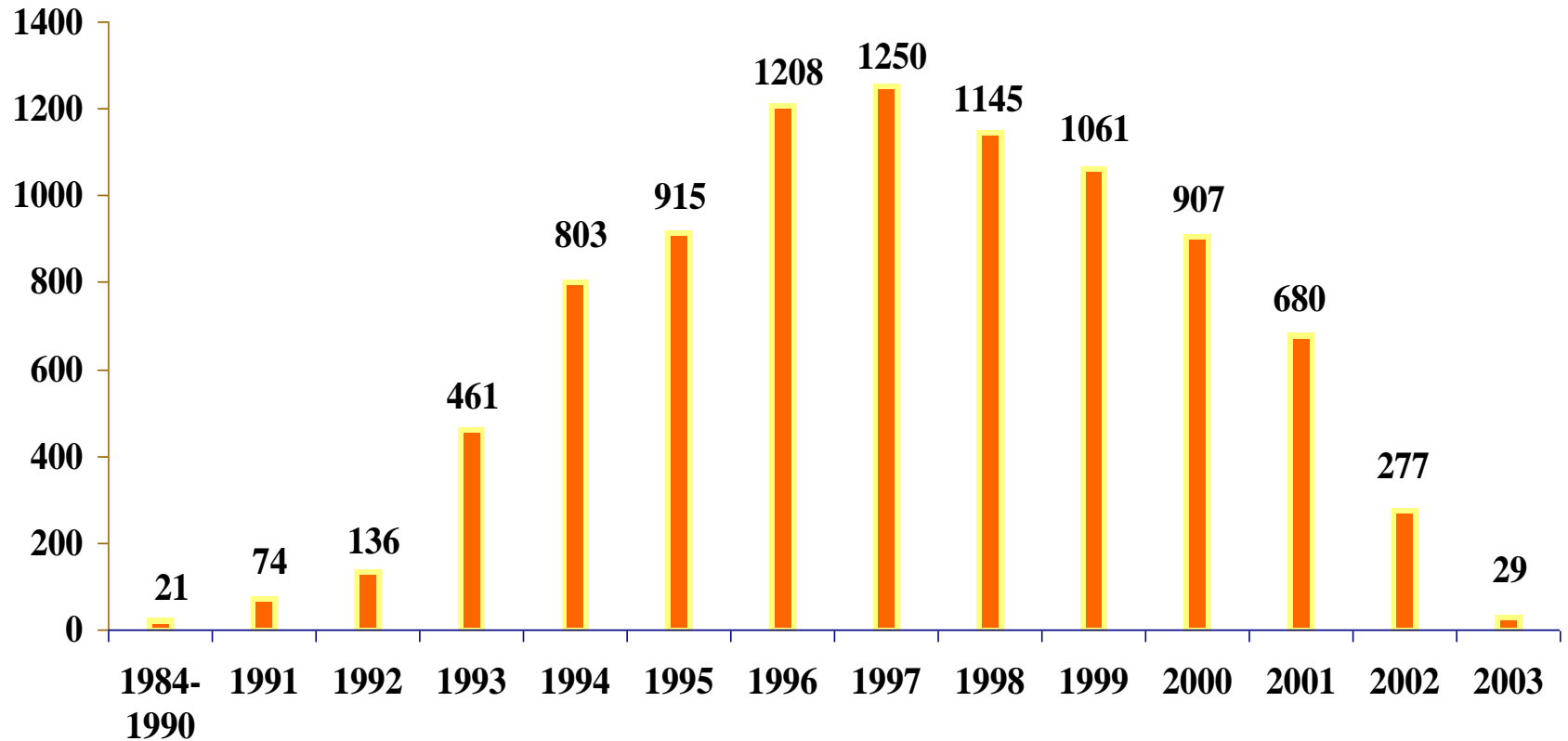


Stop



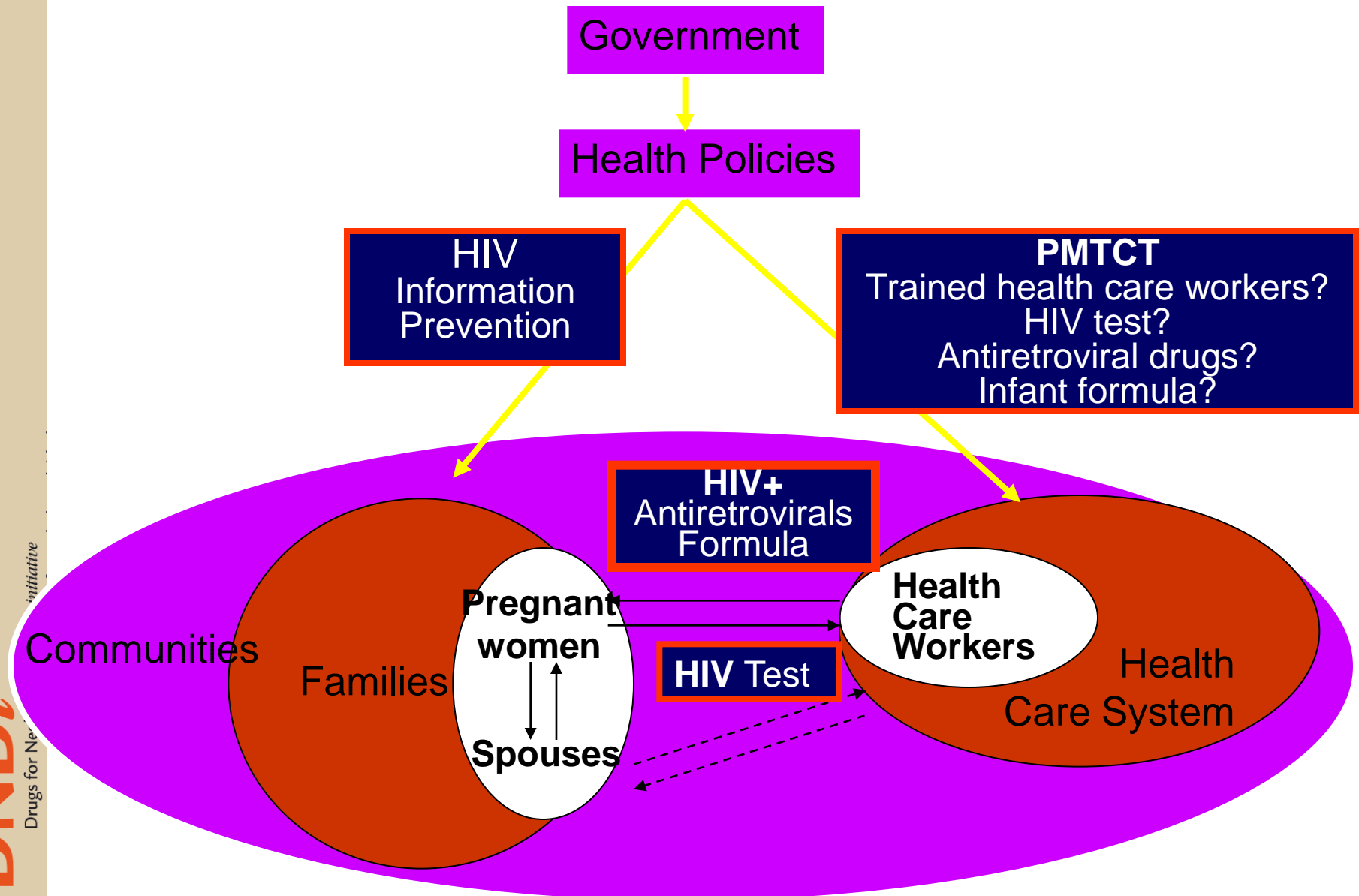
... until the child is no longer exposed to HIV

Number of AIDS Cases reported in Children 0 - 4 years, in Thailand



Thai MoPH Epidemiology Division, May 2003.

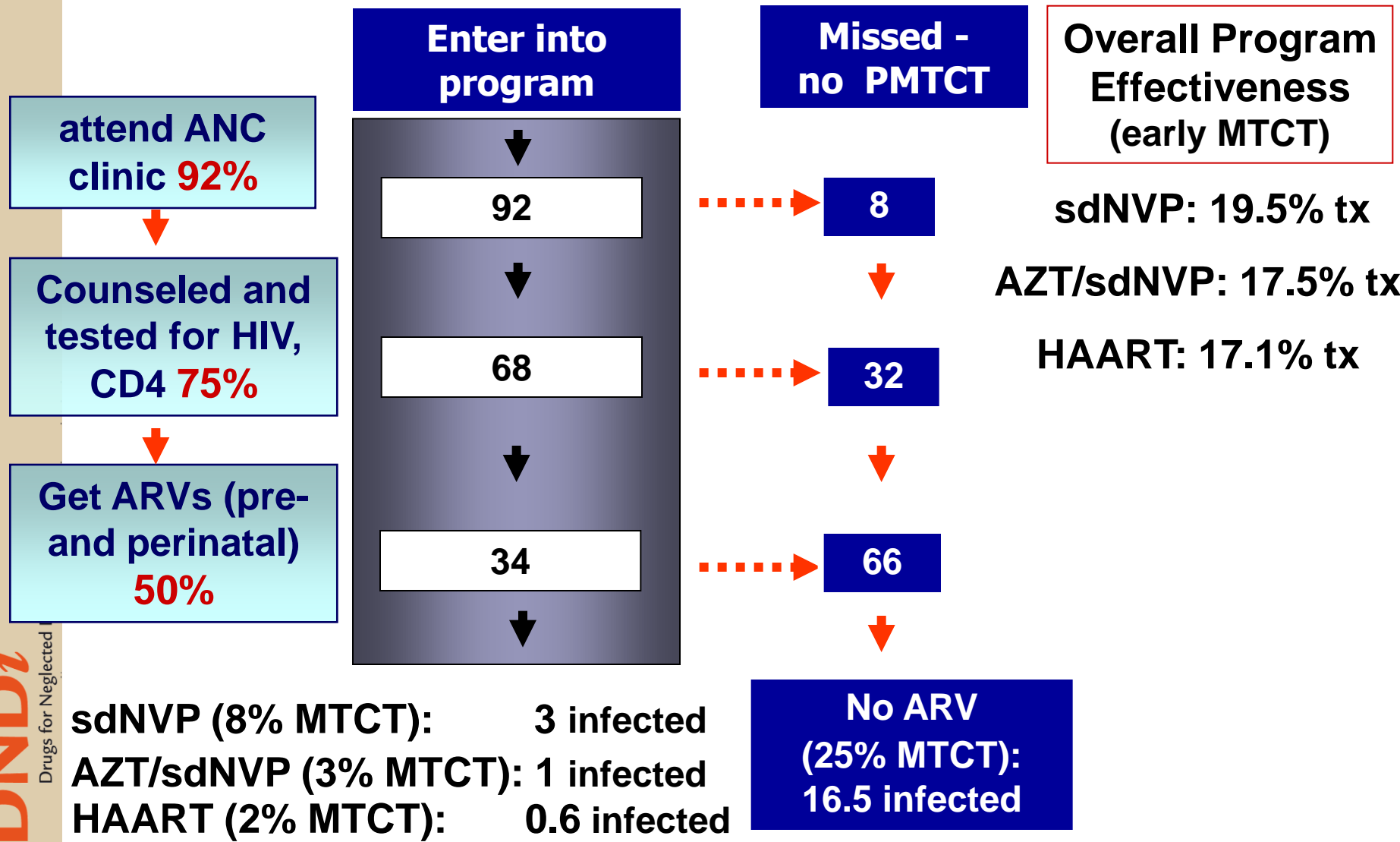
The real context of prevention of mother-to-child transmission



PMTCT Cascade: Most Critical Thing for PMTCT is Number of Women Completing Cascade

P. Barker, WHO Mtg Nov 2008

100 HIV+ mothers

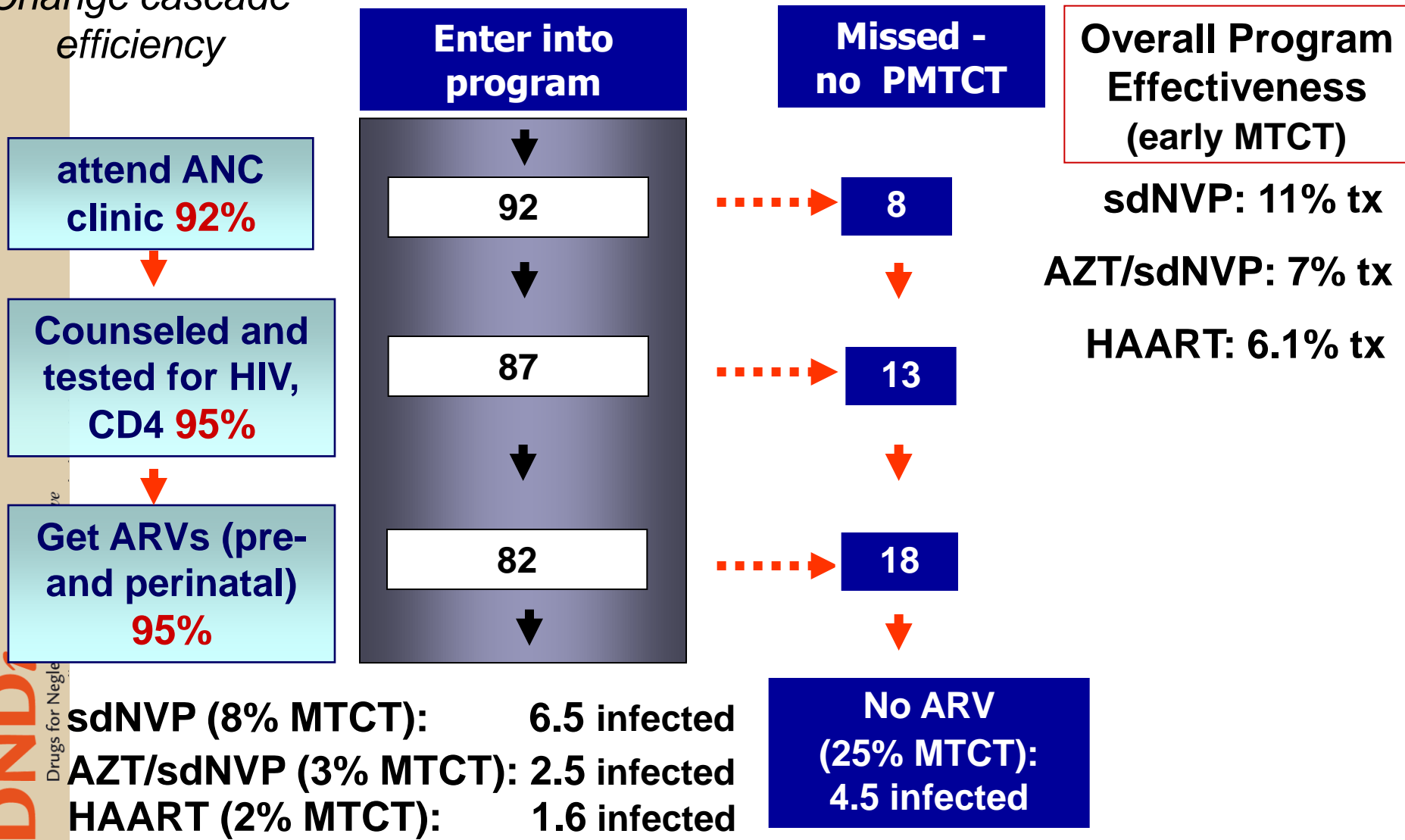


PMTCT Cascade: Most Critical Thing for PMTCT is Number of Women Completing Cascade

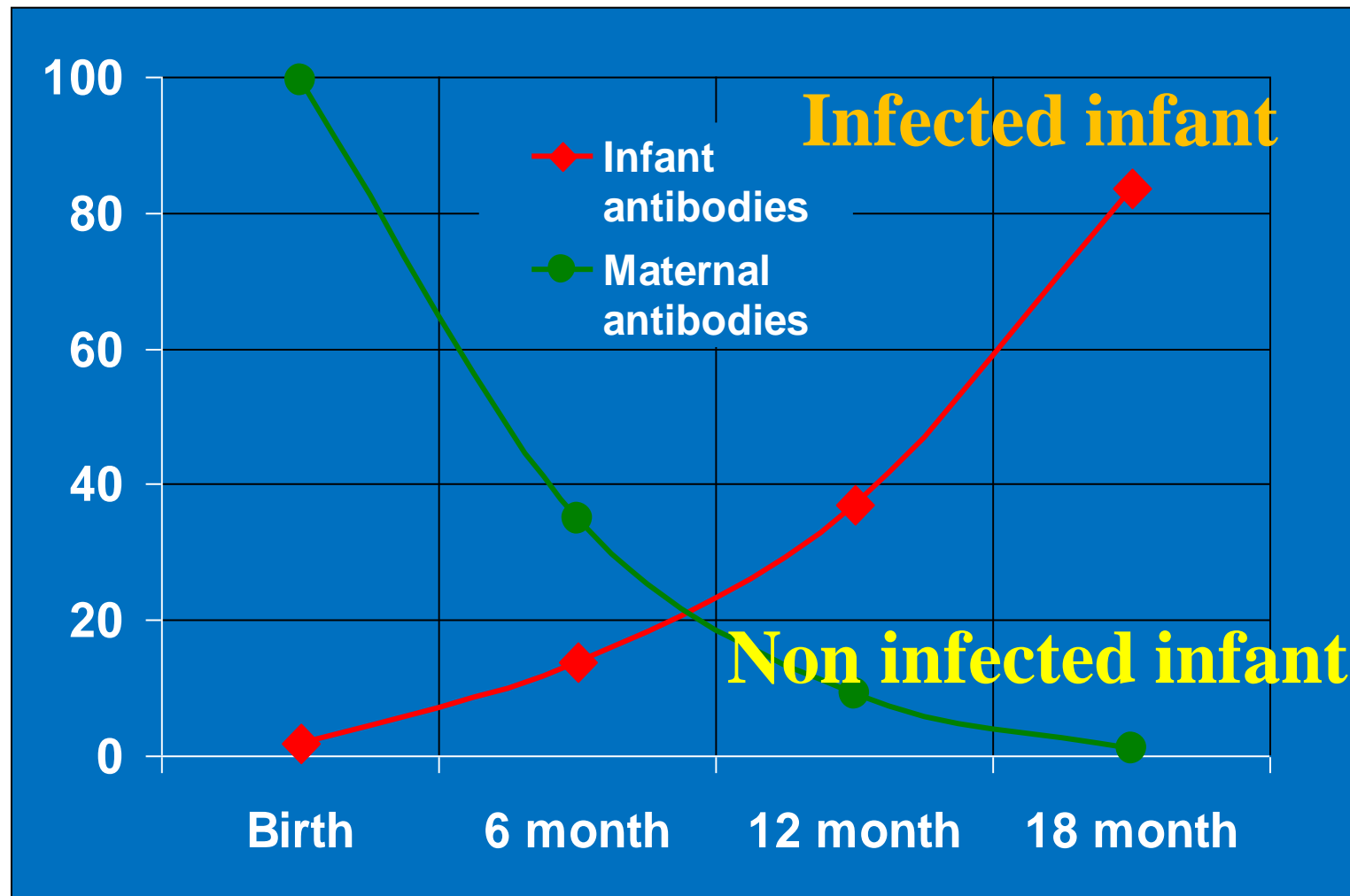
P. Barker, WHO Mtg Nov 2008

Change cascade efficiency

100 HIV+ mothers



Serological diagnosis: half of a generation of HIV infected infants has already disappeared

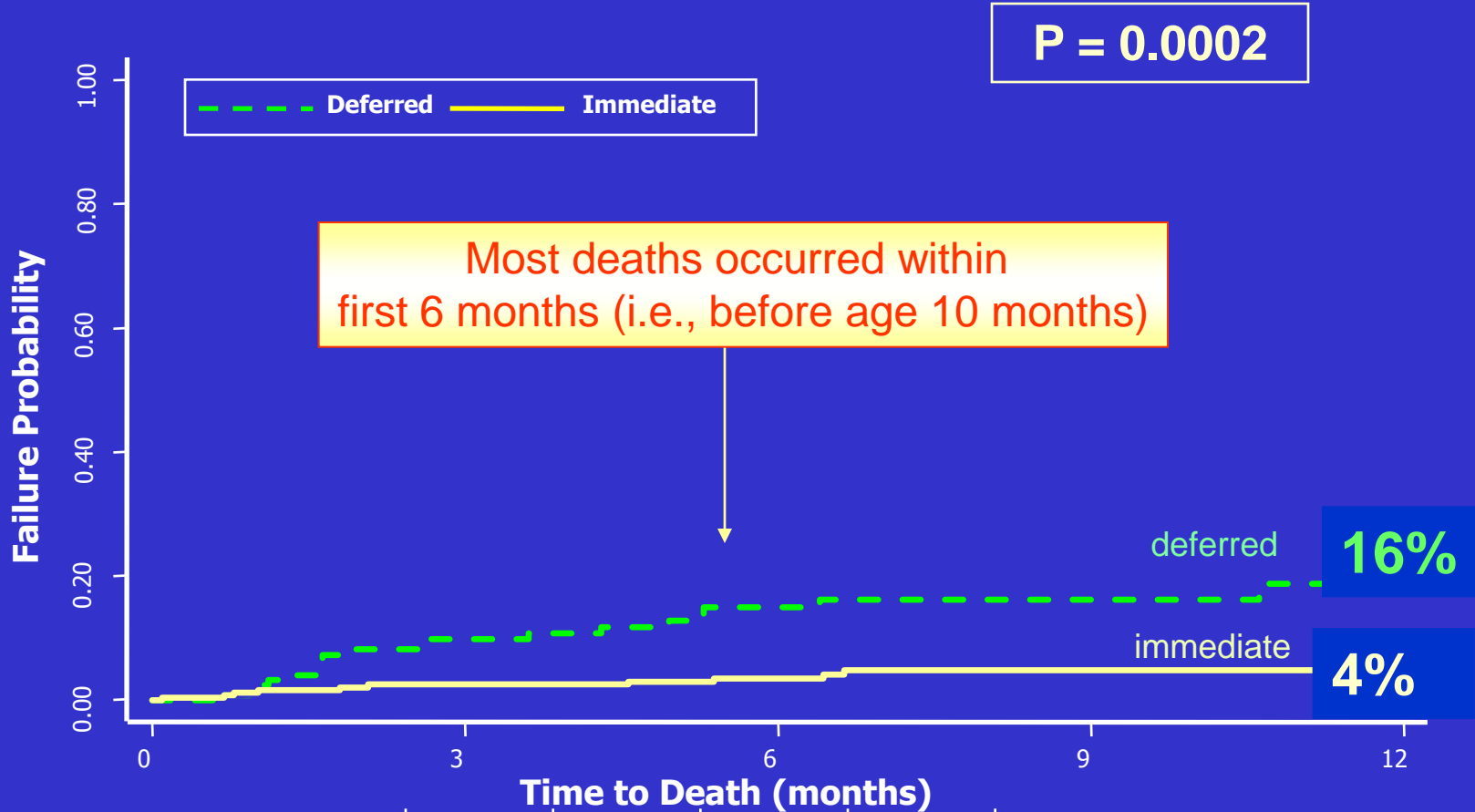


Although perinatal HIV could be quasi eliminated, the reality is that:

- Women may not know that they are infected
- They may acquire infection during pregnancy, or in the postpartum period with extremely high viral loads thus extremely high risk of transmission to the foetus/infant
- They may not be offered prevention or may present too late to fully benefit from prevention measures
- We need to continue treating an increasing number of perinatally infected infants/children

CHER trial: 76% risk of death reduction with Immediate compared to deferred HAART

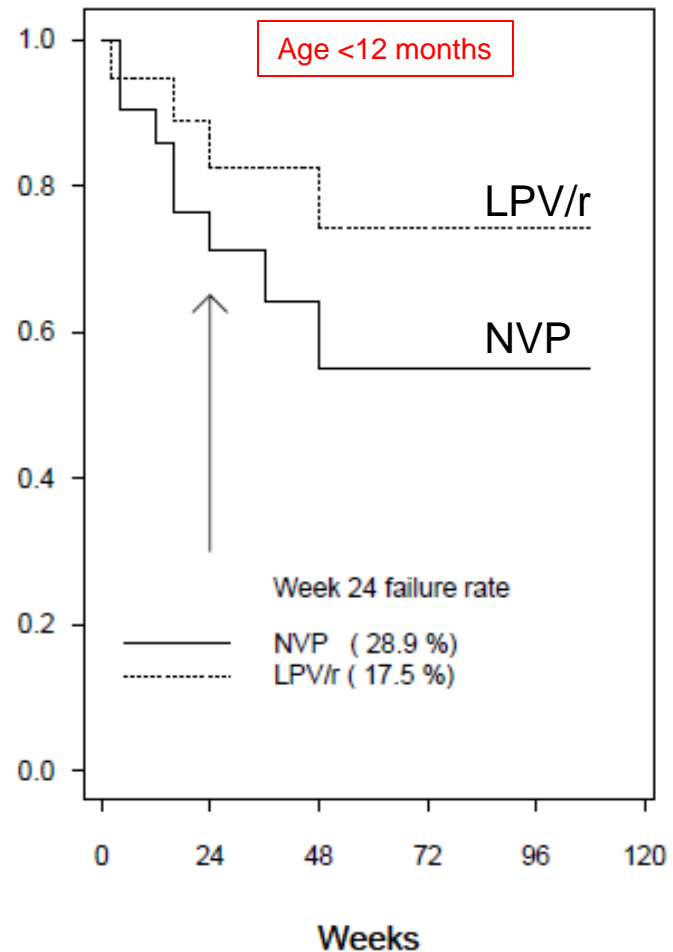
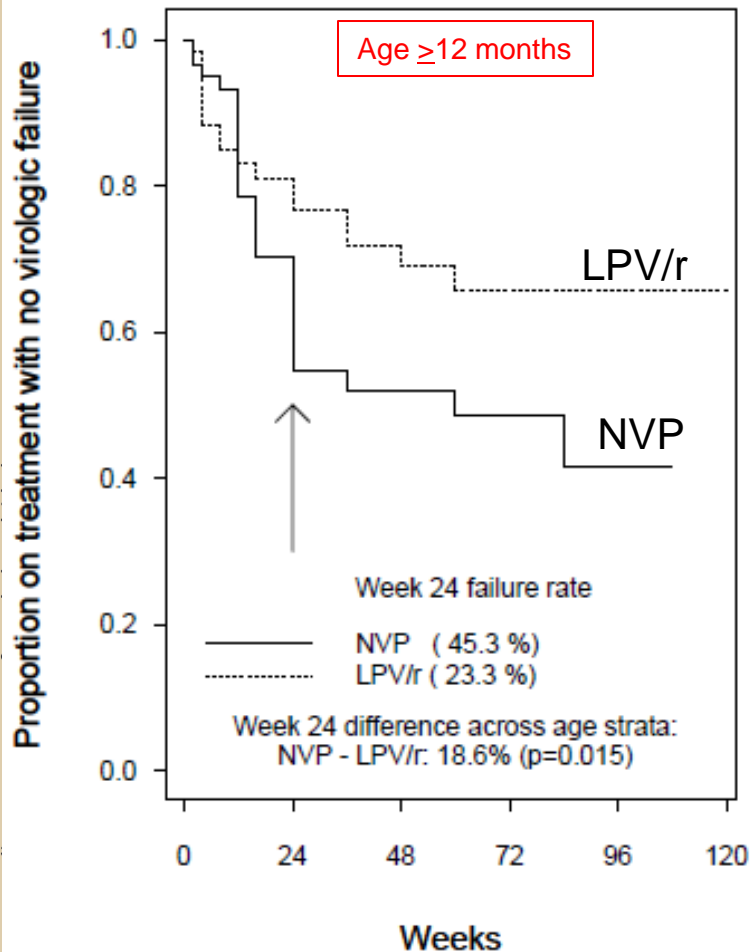
Violari A, Cotton MF, Gibb DM, et al NEJM. 2008;359(21):2233-2244.



Patients at risk	Time to Death (months)				
	Month 0	Month 3	Month 6	Month 9	Month 12
Arm 1	125	104	72	44	22
Arm 2 & Arm 3	252	213	145	99	52

P1060: LPV/r superior to NVP-Based HAART In HIV-Infected Children with sdNVP Exposure

Palumbo P et al. IAS, Capetown, South Africa, July 2009, Abs. LBPEB12

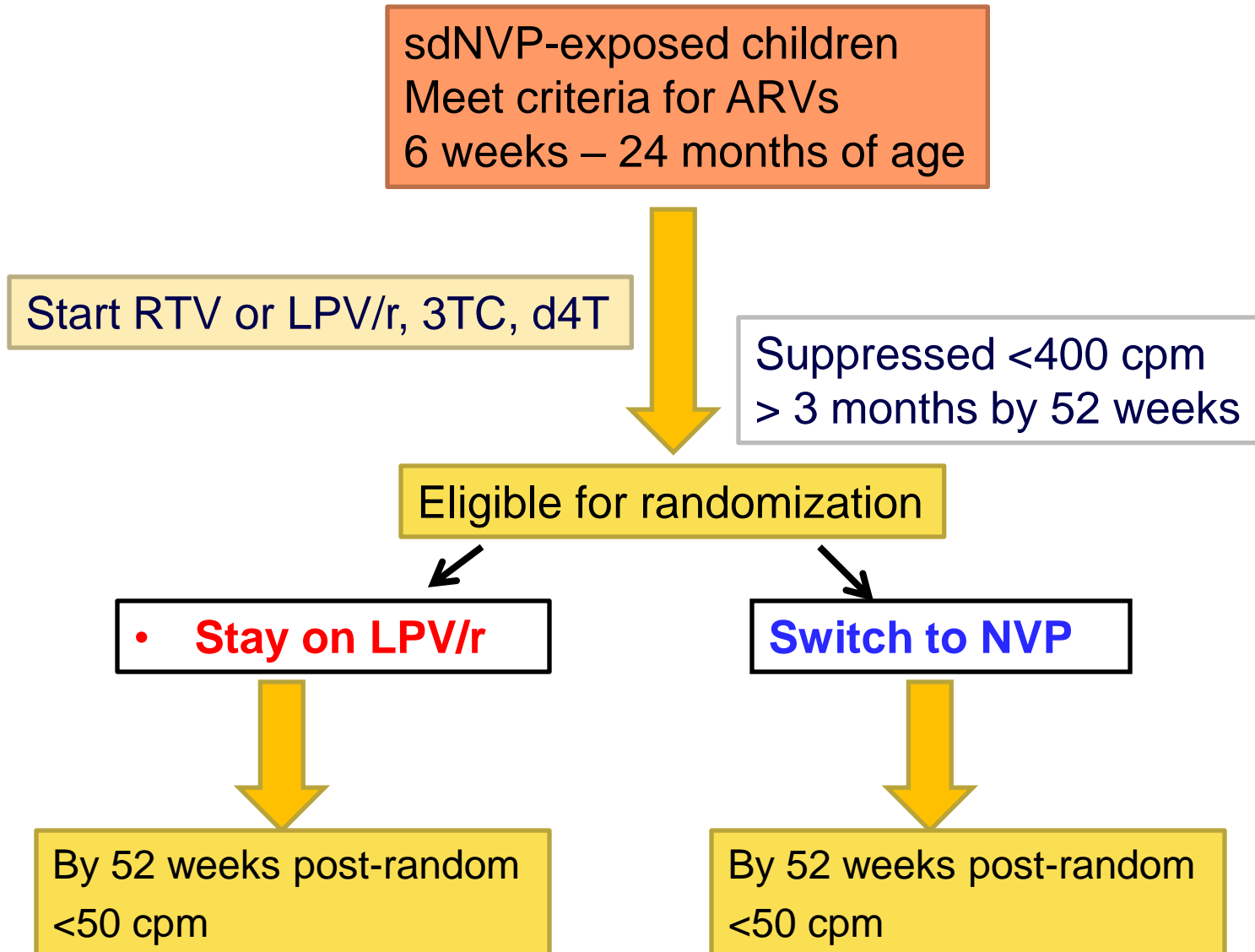


P1060: LPV/r superior to NVP-Based HAART In HIV-Infected Children **with NO NVP Exposure**

- Identical results !
 - High viral load in infants
 - Under exposure to NVP at treatment initiation ?

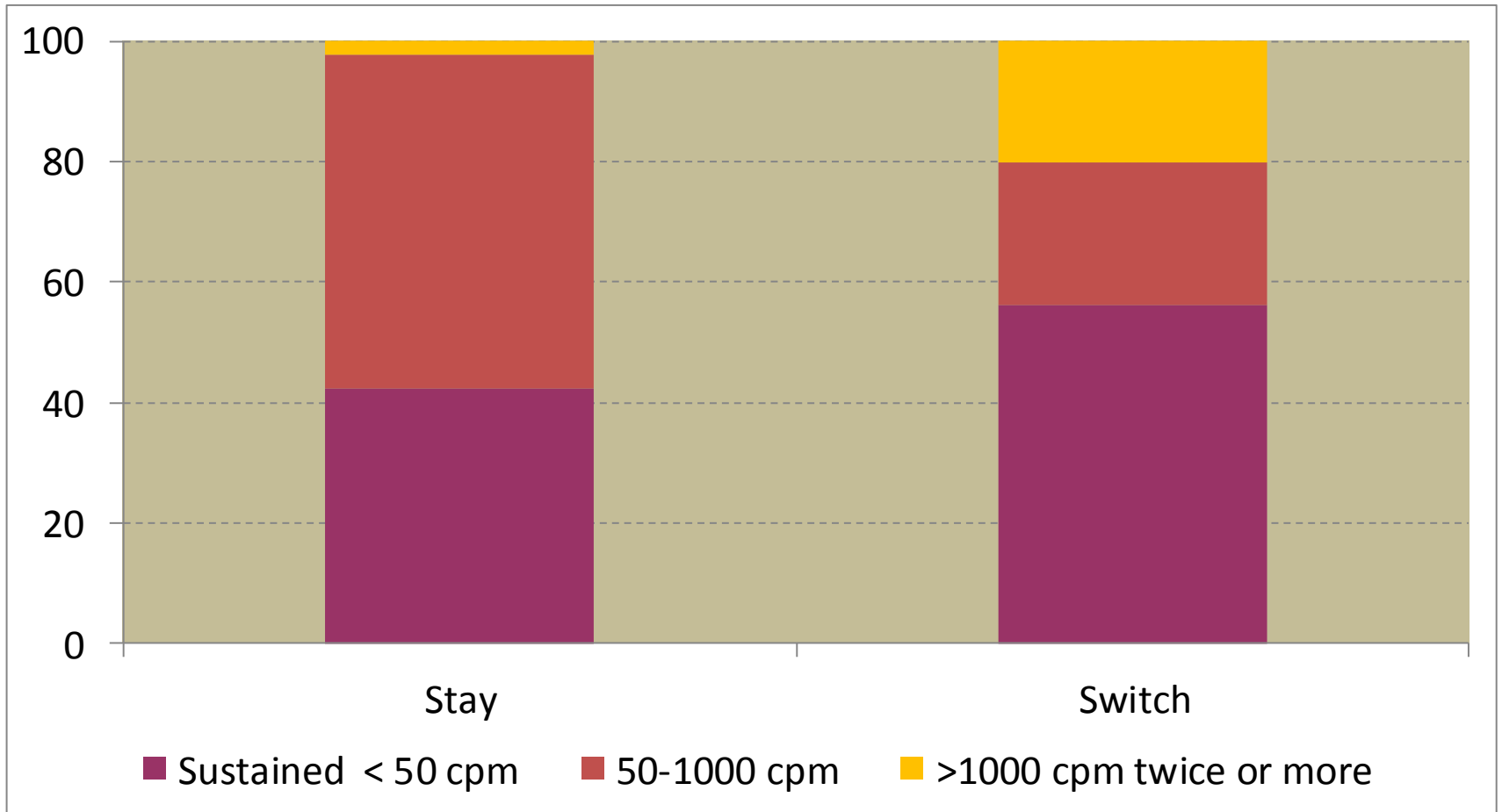
NEVEREST

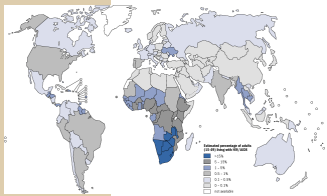
Coovadia A, Abrams EJ, Stehlau R, et al. *JAMA*. 2010;304(10):1082-1090.



NEVEREST: Patterns of viral suppression post-randomization

Coovadia A, Abrams EJ, Stehlau R, et al. *JAMA*. 2010;304(10):1082-1090.





Two Pediatric Epidemics

- High-resource countries
 - New perinatal infections are rare
 - Effective treatment available
 - Aging cohort of infected children
 - Concerns long-term complications of treatment
- Low-resource countries
 - 1,000 infants are newly infected each day
 - Diagnosis of infection in infants problematic
 - Problems with drug access
 - Treatment when available is started late

FDA Approved ARVs (as of July 2011)

-- Limited choices for neonates and infants

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Protease Inhibitors (PIs)	Integrase Inhibitor	Fusion Inhibitor	CCR5 Antagonist
Abacavir (ABC)/ Ziagen	Delavirdine (DLV)/ Rescriptor	Atazanavir (ATV)/ Reyataz	Raltegravir (RAL)/ Isentress	Enfuvirtide (T20)/ Fuzeon	Maraviroc (MVC) Selzentry
Didanosine (ddI)/ Videx EC	Efavirenz (EFV)/ Sustiva	Darunavir (DRV)/ Prezista			
Emtricitabine (FTC)/ Emtriva	Etravirine (ETR)/ Intelence	Fosamprenavir (FPV)/ Lexiva **			
Lamivudine (3TC)/ Epivir	Nevirapine (NVP)/ Viramune	Indinavir (IDV)/ Crixivan			
Stavudine (d4T)/ Zerit	Etravirine (ETR)/ Intelence	Lopinavir+ Ritonavir (LPV/r)/ Kaletra			
Tenofovir Disoproxil Fumarate (TDF)/ Viread	Rilpivirine (RIL)	Nelfinavir (NFV)/ Viracept			
Zidovudine (ZDV, AZT)/ Retrovir		Ritonavir (RTV)/ Norvir			
		Saquinavir (SQV)/ Invirase			
		Tipranavir (TPV)/ Aptivus			Not approved in neonates and infants

Delay between adult approval and pediatric determination: A pediatric antiretroviral development inertia (i-base Pipeline 2011)

P. Clyden

Drug	Calendar years	Time in years between adult approval and PD	Manufacturer
Didanosine	1991–2001	9.9	Bristol-Myers Squibb
Lamivudine	1995–2001	5.7	GlaxoSmithKline
Saquinavir*	1995–2010	14.9	Roche
Stavudine	1995–2001	5.7	Bristol-Myers Squibb
Ritonavir	1996–2005	9.3	Abbott
Nevirapine	1996–2001	5.5	Boehringer Ingelheim
Nelfinavir	1997–2003	6.5	Agouron
Abacavir	1998	<1	GlaxoSmithKline
Lopinavir/ritonavir	2000–2007	7.5	Abbott
Emtricitabine	2003–2005	2.9	Gilead
Tipranavir	2005–2007	2.7	Boehringer Ingelheim

Source: CHAI Clinton Foundation

Pediatric Treatment in Low Resource Countries

What is Available for Adults



FDCs that allow one pill once or twice daily

What has been Available for Children



Giving 3 different liquids hard to transport/store/give

Splitting adult tablets, risking inappropriate dose and associated risk toxicity or underdosing=resistance



What is Becoming Available for Children --- BUT NEED

CIPLA

D4T	30/40 mg	12 mg	6 mg
3TC	150 mg	60 mg	30 mg
NVP	200 mg	100 mg	50 mg
Ratio	1:5:6.6	1:5:8.3	

RANBAXY

Each TFOS contains:
Lamivudine 20mg + Nevirapine 35mg + Stavudine 5mg

Each TFOS contains:
Lamivudine 40mg + Nevirapine 70mg + Stavudine 10mg

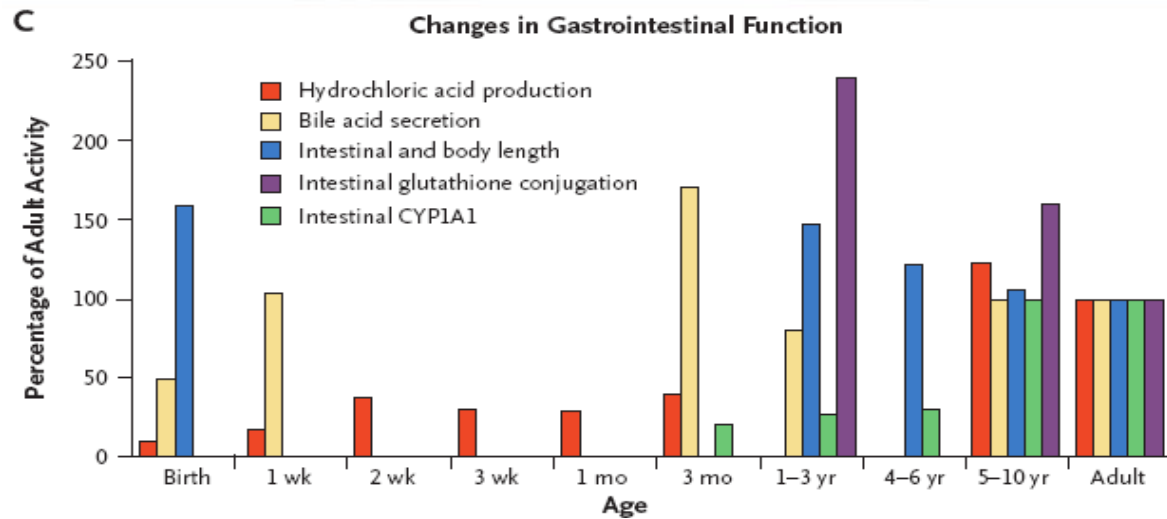
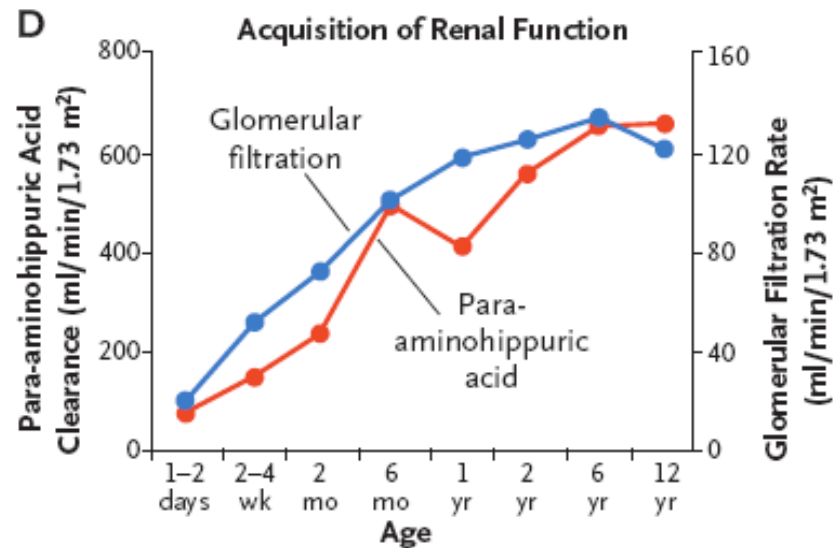
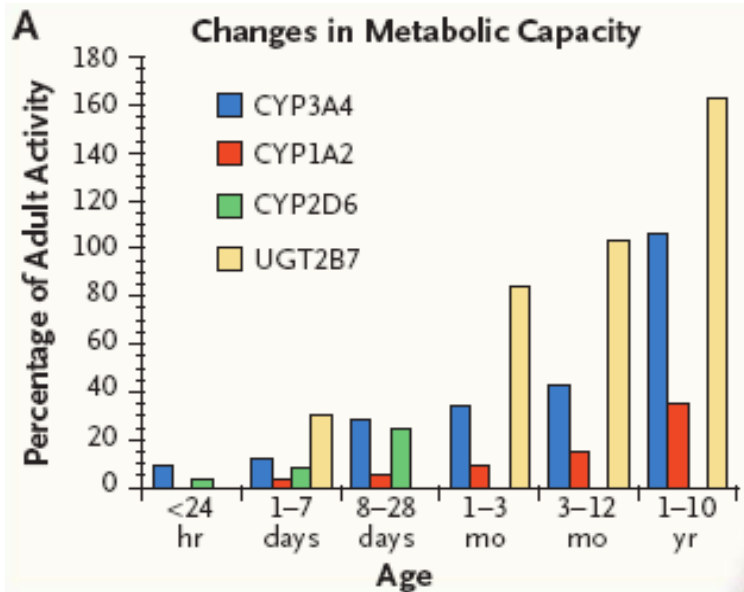
- More than d4T/3TC/NVP preparations
- Crushable and dispersible tablets/granules
- Appropriate drug ratios based on PK
- Dual as well as triple FDC
- To be affordable

Scored crushable FDCs

Adapted from L. Mofenson

Special Considerations in Pediatric ART

- Age-specific differences in CD4 T-cell counts
- Changes in pharmacokinetic parameters with age
- Differences in clinical manifestations
- Adherence issues
- Neonatal exposure to ARVs
- Diagnosis requires HIV virologic test (DNA/RNA PCR) for infants <18 months
- Very high viral loads in infants



Additional difficulties

- Enrollment and retention in treatment program
- ARV formulation: limited FDC, acceptability (taste, stability)
- PI toxicity (lipids)
- NRTI toxicity – Mitochondria, bone & renal
- Brain protection
- Virological monitoring, CD4
- TB-HIV co-infection / co-treatment
- Other comorbidities - Malnutrition, diarrhea, malaria & others
- Supply & Cost

DND*i*, a virtual non for profit R&D organization entering the paediatric HIV field

- In 2010, the Drugs for Neglected Diseases *Initiative* (DND*i*) was called upon by various organizations, including MSF, Clinton Foundation and UNITAID, to apply its expertise to address unmet needs for paediatric HIV drug R&D.
- Based on an initial needs assessment, DND*i*'s Board of Directors approved the expansion of the portfolio to paediatric HIV in December 2010.
- Since then has developed a network of paediatric HIV experts to advise on its R&D strategy

DNDi Project Portfolio – June 2011

Discovery

HAT LO Consortium
 - *Scynexis*
 - *Pace Univ.*

VL LO Consortium
 - *Advinus*
 - *CDRI*

Chagas LO Consortium
 - *CDCO*
 - *Epichem*
 - *Murdoch Univ.*
 - *FUOP*

Major Collaborators:

- Sources for hit and lead compounds:
GSK, Anacor, sanofi aventis, Merck, Pfizer, Novartis (GNF, NITD), TB Alliance,...
- Screening Resources:
Eskitis, Institut Pasteur Korea, Univ. Scynexis, U. Dundee,...
- Reference screening centres:
LSHTM, Swiss Tropical & Public Health, University of Antwerp

Pre-clinical

Nitroimidazole backup (HAT)

Oxaborole SCYX7158 (HAT)

Alternative formulations of Amphotericin B (VL)

Nitroimidazole (VL)

Drug combination (Chagas)

K777 (Chagas)

Flubendazole
 Macrofilaricide (Helminth)

Exploratory

Clinical

Fexinidazole (HAT)

New VL treatments –
 Bangladesh

New VL treatments –
 Africa

New VL treatments –
 Latin America

Benznidazole
 Paediatric dosage form
 (Chagas)

Azoles E1224
 & Biomarker (Chagas)

Paediatric HIV
 (exploratory)

Exploratory

Implementation

ASAQ (Malaria)
 Fixed-Dose Artesunate/ Amodiaquine

ASMQ (Malaria)
 Fixed-Dose Artesunate/ Mefloquine

NECT (Stage 2 HAT)
 Nifurtimox – Eflornithine
 Co-administration

SSG&PM co-administration
 VL in Africa

New VL treatments in Asia
 (SD AmBisome[®],
 PM+M / A[®]+M / PM+ A[®])

Scope of projects

- First-line cART for “under 3 year olds”
- Short-term (< 3 yr) and medium-term (< 5 yr) projects
- Guided by Target Product Profile (TPP)

Target Product Profile

Profile	Ideal	Acceptable
Target population	Both NVP-exposed and non-exposed HIV+ children under 3 year old	
Dosing frequency	Once-daily	Twice-daily
Formulation	Water-soluble, dispersible tablet dosage form that can be used with small amount of liquid (suitable for 2 to 36 months old)	Sprinkles dosage form may work. ^a Crushable pill that can be used in "food" may be acceptable
Pill burden	1 (scored) pill - usable across broad weight bands (WHO table)	If 2 pills, must be same tablet count (or same fraction) for both
Durability ^d	High genetic barrier (PI-like). Long plasma half-life.	
Efficacy	Same as for adults	
Safety/tolerability	Well tolerated and no laboratory monitoring needed	No laboratory monitoring needed
Palatability (taste)	No taste or nice taste for children	Palatable
Drug-drug interaction (TB Rx)	No drug-drug interaction with TB medicines, particularly rifampicin or rifabutin	Some drug-drug interaction with TB medicines, but can be used with proper dose adjustments
Stability	No cold chain requirement, minimum 2 years shelf life at room temperature	
Cost	≤ 50 USD/patient/year (consistent with adult ART) ^b	To be investigated ^c

Summary of actions planned

- PI: LPV/r, (ATV/r)
- NRTI: ABC, ZDV, TDF?
- TB coinfection
 - Changing TB treatment: Rifampicin replacement
 - Changing ARV regimen: Super-boosting (RTV)
- Induction-maintenance:
 - raltegravir, (dolutegravir)
 - place of etravirine/rilpivirine vs NVP in a «NEVEREST» induction/maintenance concept

Projects under consideration (1)

- PI-based 1st line
 - Prodrugs: for ritonavir (RTV) & lopinavir (LPV)
 - Synthesis commissioned
 - Characterization planned (PK, stability formulation, etc.)
 - Improved formulation with existing API
 - Nanodispersion formulation
 - Nanoparticles
 - Uncertainties:
 - Taste
 - Cost
 - Intellectual Property

Projects under consideration (2)

- N(t)RTI (Nucleos[t]ide reverse transcriptase inhibitor) options:
 - AZT/3TC (current choice in US & Europe)
 - FDC in dispersible tablet form is available (AZT a 'fading' choice in adult ART, better used after TDF?)
 - ABC/3TC (choice in SA)
 - Current first-line paediatric in So. Africa
 - Rare ABC hypersensitivity (HLA-B*5701 haplotype) in African population (0.3%)?
 - Cost ?
 - TDF/3TC (preferred, if safe in <2 yo)
 - TDF has been filed for approval for 2-6 year olds (Gilead)
 - Aligned with adult ARV preference
 - Safety in under 2 unclear (bone and renal)

Projects under consideration (3)

Incompatibility between ARV & TB medicine

- *Rifampicin induced CYP3A4 expression*
 - *PIs and some NNRTIs are metabolized mainly by CYP3A4*
 - *RTV inhibits CYP3A4, thus enhances PI exposure*
 - *Extra RTV (superboosting) is required when rifampicin is given*
-
- TB medicine that is compatible with ARVs
 - Rifabutin or rifapentine as alternative for rifampicin
 - To hold expert meeting with TB Alliance
 - To facilitate the development (long-term)
 - ARV regimen that is compatible with TB treatment
 - RTV for superboosting
 - Raltegravir + TDF/3TC adult trial in Brazil (Merck-Gilead)

Projects under consideration (4)

- Improved forms of ritonavir for superboosting
 - Prodrug of ritonavir (RTV)
 - Involves chemical modification
 - Potential for dispersible tablet
 - Nanodispersion formulation of RTV
 - Technology is based on the formation of a dry, solid blend of insoluble material within a soluble matrix without the need for chemical modification
 - Nanoparticles

Projects under consideration (5)

- “*Induction-Maintenance*” scheme
 - HIV+ children have higher viral load, and unpredictable disease progression
 - NEVEREST concept: initiating therapy with a boosted PI then switching to a safe/easy to use regimen after reduction in viral load
 - Integrase inhibitors achieve HIV RNA levels below detection at a more rapid rate than other drugs
 - Raltegravir is the top choice, but not yet approved for infants
 - New integrase inhibitor Dolutegravir?
 - Second generation NNRTIs
 - Etravirine (does it retain efficacy after induction in NVP exposed infants for PMTCT infected by a non subtype B HIV?)
 - Rilpivirine (id ?)

Thank you very much for your
attention



Best
science
for the
most
neglected