

Issues in the Treatment of Pediatric HIV in the Resource Limited Setting

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December 2007



Outline

- A brief history of the epidemic in children
- Challenges in care and antiretroviral treatment
- Reports from the roll out ...
- Future Directions



The beginning (in the USA)



- 4 infants with immunodeficiency in 1982 in New York, New Jersey, and San Francisco ⁽¹⁾
- First transfusion associated case described in 1983 at UCSF ⁽²⁾

(1) MMWR 1982; 31(49): 665-7.
(2) MMWR 1983; 1(831) 956-8.

As of 2005 ...



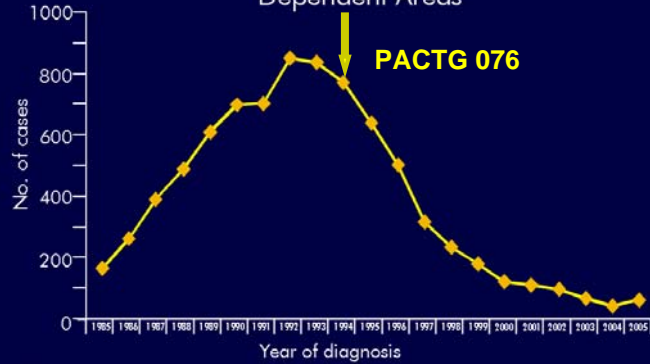
Reported AIDS Cases in Children <13 Years of Age
by Transmission Category, 2005 and Cumulative
United States and Dependent Areas

Transmission Category	2005		Cumulative	
	Number	%	Number	%
Perinatally acquired	86	92	8,637	91
Transfusion-associated	0	0	386	4
Hemophilia	0	0	230	2
Other/not reported	7	8	188	2
Total	93	100	9,441	100



Perinatal AIDS Cases

Estimated Number of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2005—United States Dependent Areas

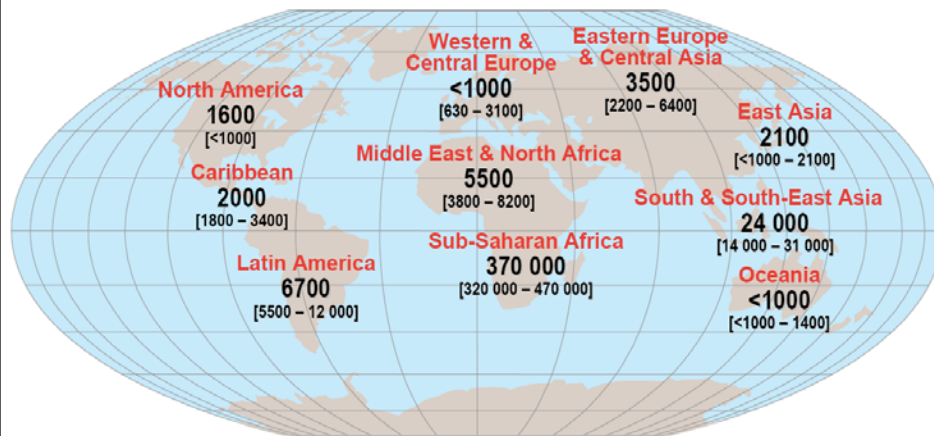


Note: Data adjusted for reporting delays and cases without risk factor information were proportionally redistributed.



www.cdc.gov/hiv/topics/surveillance/resources/slides/pediatric/index.htm

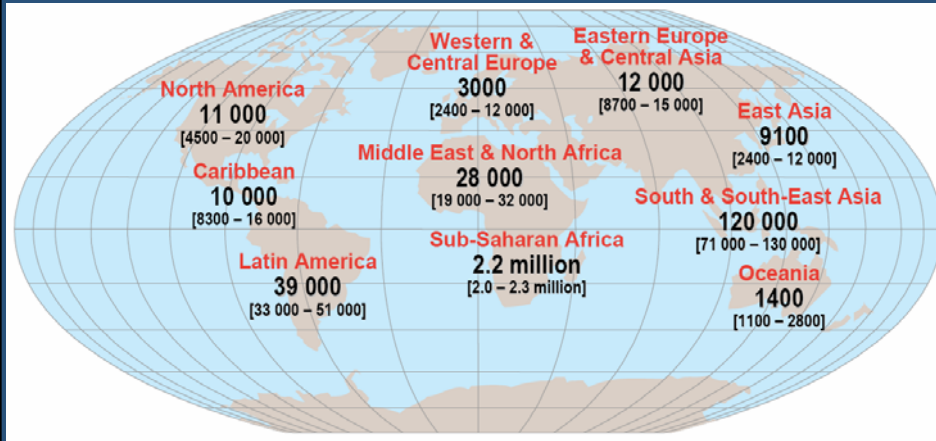
Children (<15 years) newly infected with HIV in 2007



Total: 420 000 (350 000 – 540 000)

www.unaids.org/en/HIV_data/2007EpiUpdate/

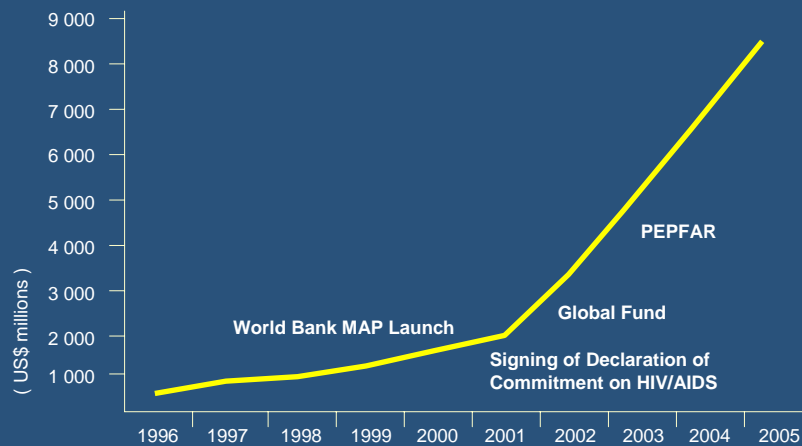
Children (<15 years) living with HIV in 2007



Total: 2.5 (2.2 – 2.6) million

www.unaids.org/en/HIV_data/2007EpiUpdate/

Estimated total annual resources available for HIV/AIDS, 1996–2005



Lancet, 2006; 368: 526–30

Overall Access to ART in 2005



Geographical region	Number receiving ART	Estimated need	Coverage
Sub-Saharan Africa	1 040 000	4 600 000	23%
Latin America and the Caribbean	345 000	460 000	75%
East, South and South-East Asia	235 000	1 440 000	16%
Europe and Central Asia	24 000	190 000	13%
North Africa and the Middle East	4 000	75 000	5%
Total	1 650 000	6 800 000	24%

UNAIDS, 2006

Children (<15 years) receiving and needing ART, December 2006



Geographical region	Estimated number receiving ART	Estimated need	Coverage
Sub-Saharan Africa	85 000	680 000	13%
Latin America and the Caribbean	15 500	23 000	67%
East, South and South-East Asia	13 300	64 000	21%
Europe and Central Asia	1 500	7 500	20%
North Africa and the Middle East	<100	10 000	<1%
TOTAL	115 500	780 000	15%

WHO, 2007

Pediatric Roll Out – Funding and implementation



- PEPFAR
- Global Fund

- Clinton Foundation HIV/AIDS Initiative
- Elizabeth Glaser Pediatric AIDS Foundation
- Baylor International Pediatric AIDS Initiative
- National Programs

“Ten Point Management Plan”



- **Early Diagnosis of HIV infection**
- **OI Prophylaxis and treatment**
- **Antiretroviral therapy as indicated**
- Immunizations
- Growth and development monitoring
- Nutrition education and supplementation
- Psychosocial support
- Aggressive treatment of acute infections
- Adolescent care, treatment and support
- Mother and family care and treatment MTCT plus

Department of Pediatrics, Makerere University Kampala, Uganda

Challenge and importance of early diagnosis



- Many children only tested because they become symptomatic
- Diagnosis in < 18 mo difficult
 - Antibody based testing not reliable
 - DNA or P24 Ag testing limited
- *Why it is so urgent ?*

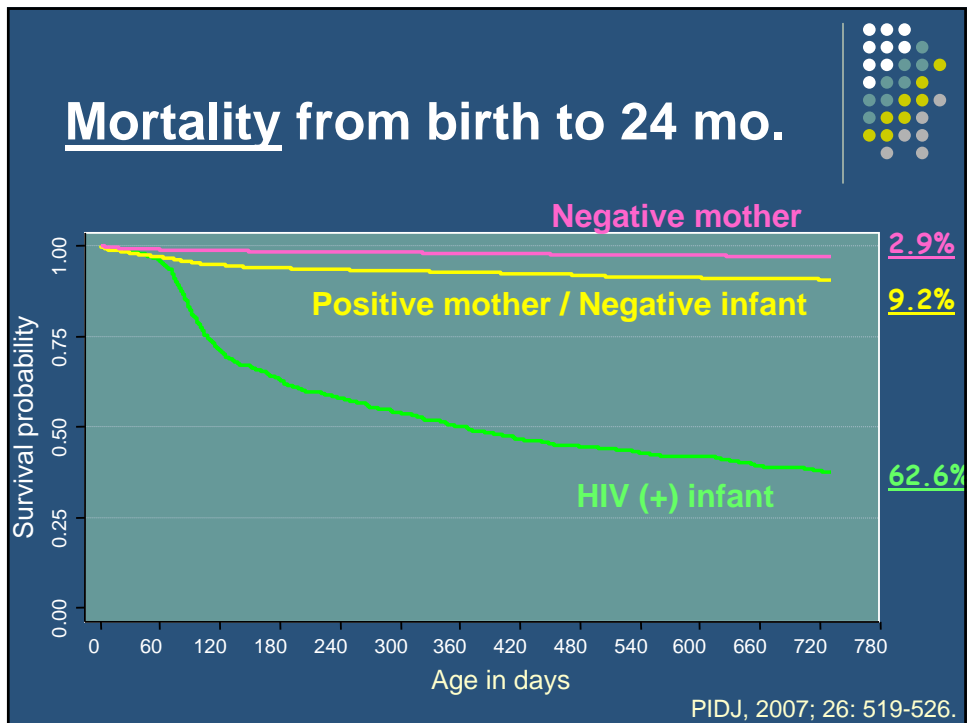
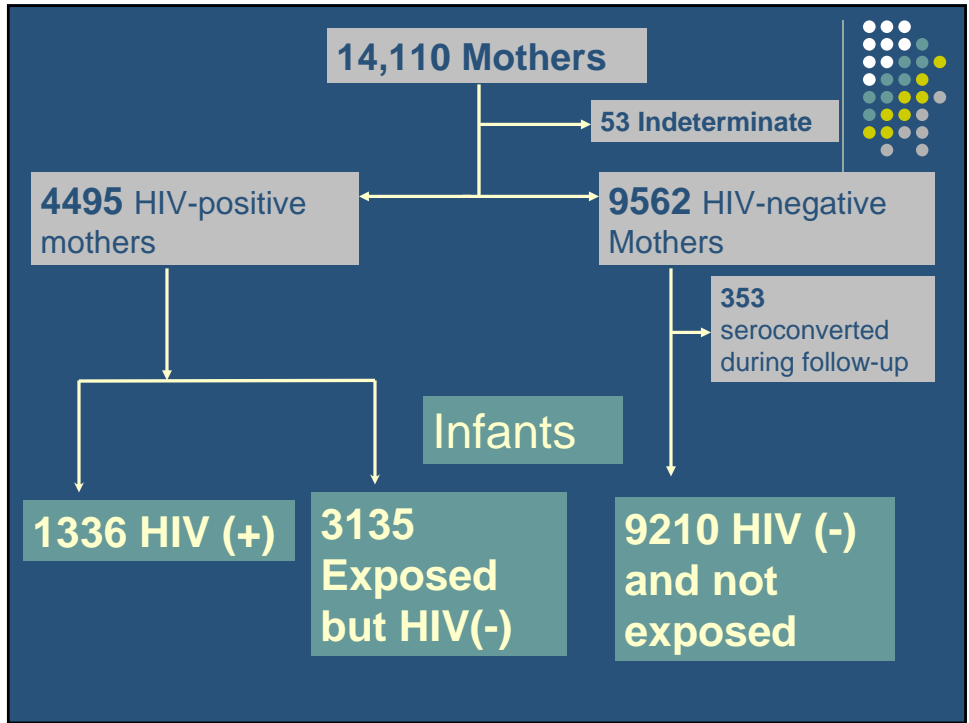
Child mortality according to maternal and infant HIV status in Zimbabwe



E Marinda, J Humphrey, P Iliff,
K Mutusa, E Piwoz, L Moulton, K
Nathoo, P Salama, B Ward

ZVITAMBO Study Group





How do you deal with this ?



- Increase testing and diagnosis ...
 - Coordinated PMTCT programs
 - Active testing program in communities (eg Whole families)
 - DBS based DNA testing
- OI prophylaxis
- Antiretroviral Therapy
 - WHO Guidelines - other reasons to start
 - When to start?

“CHAP”



- **Cotrimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial**
- Chintu C, Bhat GJ, Walker AS, Mulenga V, Sinyinza F, Lishimpi K, Farrelly L, Kaganson N, Zumla A, Gillespie SH, Nunn AJ, Gibb D.

CHAP



- Double-blind randomized placebo-controlled trial of co-trimoxazole vs placebo
- 534 HIV infected children
- 1-14 years
- University Teaching Hospital, Lusaka, Zambia
- Diversity of age and cd4, minority on ART (5-10%)

Lancet 2004;364:1865-1871

CHAP



- **Death rate at median 19 mo f/u**
 - 74 (28%) children in co-trimoxazole group
 - 112 (42%) in the placebo group
 - Hazard ratio [HR] 0.57 [95% CI 0.43–0.77] p=0.0002.
- Hospital admission rate (per child-year of follow-up)
 - 48% in the co-trimoxazole group
 - 63% in the placebo group (0.77 [0.62–0.95]; p=0.01).

CHAP - consequence



- Study stopped by DSMB in October 2003
- In 2004 WHO changed recommendations to include all HIV infants up 18 mo and any “symptomatic” HIV infected child with
- In 2006, WHO recommended for all children regardless of immune or clinical status ...

Children with HIV and Malaria Project (CHAMP)



- Study of interactions between HIV and Malaria in children
- 300 HIV infected children recruited from pediatric HIV clinic at Mulago Hospital, Kampala, Uganda
- Parallel Cohort of 600 HIV (-) from same locale

Children with HIV and Malaria Project (CHAMP)



- 9 episodes of malaria among HIV-infected children (0.07/py)
- 440 episodes among children from the community (0.90/py)

- Insecticide-treated bednets (ITN)
 - 43% reduction in malaria incidence ($P < 0.001$)

- Combination of TMP/SMX + ITN
 - 97% reduction in malaria incidence ($P < 0.001$)

- *Malaria accounted for only 4% of febrile episodes in the HIV cohort in comparison with 33% in the community-based cohort ($P < 0.0001$).*

AIDS, 2007; 15: 2059-66

INH Prophylaxis



- Recommended in HIV-infected adults and children with pos. PPD skin test in USA

- Most national TB programs recommend INH for children < 5 yrs exposed to an adult with sputum + TB

- HIV infected children at **high risk** of developing TB

- No standard recommendation of INH in HIV infected children worldwide ...

Benefit of INH prophylaxis



- Isoniazid or placebo given with co-trimoxazole either daily or three times a week
- 263 children
 - 132 Received INH
- Median f/u 5.7 (2 - 9.7) months
- **Mortality 8% in INH and 16% Placebo Arms**
 - HR 0.46 by intention to treat analysis
 - TB incidence 5 cases INH and 13 cases PL (HR 0.28 p=0.005)

BMJ. 2007; 334(7585):136.

ART Initiation Guidelines – WHO (2006)



- Ideally CD4% and Clinical Stage
- Total Lymphocyte Count if CD4 not available
- Guidelines for “Presumptive” diagnosis in < 18 mo

ART Initiation Guidelines – WHO (2006)



Immunological marker ^a	Age-specific recommendation to initiate ART ^b [A (I)]*			
	≤11 months	12 months to 35 months	36 months to 59 months	≥5 years
%CD4+ ^c	<25%	<20%	<15%	<15%
CD4 count ^c	<1500 cells/mm ³	<750 cells/mm ³	<350 cells/mm ³	<200 cells/mm ³

ART Initiation Guidelines – WHO (2006)



WHO paediatric stage	Availability of CD4 cell measurements	Age-specific treatment recommendation [A (II)]*	
		≤11 months	≥12 months
4 ^a	CD4 ^b	Treat all	
	No CD4		
3 ^a		Treat all	Treat all, CD4-guided in those children with TB, ^c LIP, OHL, thrombocytopenia
	No CD4		Treat all ^c
2	CD4 ^b	CD4-guided ^d	
	No CD4	TLC-guided ^d	
1	CD4 ^b	CD4-guided ^d	
	No CD4 ^b	Do not treat	

Presumptive diagnosis of severe HIV disease



- **Confirmed** HIV antibody-positive AND
- Diagnosis of any AIDS-indicator condition can be made OR the infant is symptomatic with two or more of the following:
 - oral thrush
 - severe pneumonia
 - severe sepsis

Challenge



- Recognizing that high first year mortality many providers in USA will start any HIV infected children less than 1 year of age ...
- But in RLS it is rare to be able to confirm diagnosis and those indications are non-specific, can you really start them all on ARV presumptively? And at what cost?
- Concerns of toxicity, drug resistance early in life, limited second line options ...

Early vs. Deferred Treatment?



- Children with HIV Early ART (CHER)
 - South Africa
 - Recognition that CD4 and viral load poor predictors of disease progression in infants
 - Hypothesis: early ART with subsequent treatment interruption will delay disease progression and chronic ART
 - All healthy children < 12 weeks old with CD4% > 25%

Violari A, et al. IAS 07, WESS103.

Children with HIV Early ART (CHER)



Arm 1
Deferred ART

Arm 2
Short-course until 1y

Arm 3
Long-course until 2y

Treat, stop, and ART (re-start) when
CD4% < 20% or
clinical event (< 25%)

Follow-up for ≥ 3.5 years

Violari A, et al. IAS 07, WESS103.

CHER - Interim Analysis



	<u>Arm 2 & 3</u> <u>Treatment arms</u>	<u>Arm 1</u> <u>Deferral arm</u>
N =	252	125
Died (%)	10 (4)	20 (16)
Person years of follow-up	167	79
Death Rate/ 100 PY (95% CI)	<u>6.0</u> (2.9, 10)	<u>25.3</u> (15.5, 39.0)
Hazard ratio*	0.24 (0.11, 0.51)	

Violari A, et al. IAS 07, WESS103.

CHER - Implications



- 75% reduction in mortality in infants started on ART at <12 weeks
 - DSMB closed deferral arm
- Impact on guidelines
 - Capacity issues: diagnostics, access to pediatric ARVs
 - Clinical issues: non-African settings, treatment interruption, consequences on long-term toxicity and resistance

When to start ...



- Wait even longer? PREDICT study
 - Randomized trial of children with moderate immune failure (CD4 15-24%)
 - Immediate vs. deferred (<15%) ART

Which ARV to start ...



- Standard first-line, WHO 06
 - 2 NRTI: AZT or d4T or ABC and 3TC
 - 1 NNRTI: NVP or EFV
- NRTI
 - Generally AZT unless anemic, then d4T
 - *Thailand: 57% of children on d4T regimen had lipodystrophy by 144 weeks***
- Post NVP ART (IMPACT 1060)

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

Other issues with Pedi ART



- Inadequate number of trained health care workers comfortable with treating children
- Adherence dependant on the caregiver who may change from time to time
- Weight based dosing
 - Liquid suspensions
 - Expensive, harder to ship/distribute/store
 - Issues of compliance
 - Split adult tablets
 - Inappropriate doses for small children (<10kg)

Pill Cutting ...



Reports from the rollout...



- Concerns about how well ART with children in these settings would work ...
- Reports from:
 - BAPAI
 - Cote D'Ivoire
 - GHESKIO
 - Uganda

Baylor International Pediatric AIDS Initiative (BAPAI)



- Well resourced programs
- 10,000 children in Botswana, Uganda, Lesotho, and Malawi
- Botswana
 - 81% undetectable (<400 copies/mL) at 12 mo

Côte d'Ivoire



- National treatment program
- 395 children
 - 80% had a CD4% <15%, Median RNA 5.6 log
 - Median age was 7 years
- 54% undetectable at 12 mo

Nkengasong JN, Adje-Toure C, Hanson D, et al. Virologic and Immunologic Response to ART and Predictors of HIV-1 Drug Resistance in Children Receiving Treatment in Abidjan, Côte d'Ivoire. CROI 2007.

South Africa



- Sinikithemba HIV/AIDS clinic in KwaZulu-Natal, South Africa
- 151 children
 - median age 5.7 years (range 0.3–15.4)
 - median follow-up time 8 months
- At 6 mo, 84% undetectable (< 50 c/ml)
- At 12 months, 80.3% undetectable (< 50 c/ml)

Reddi et al. BMC Pediatr 2007;7:13

Haiti



- Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO), Haitian NGO
- 236 children started ART
 - Median viral load 5.30 log c/mL
- 56% (56/100) undetectable (< 50c/ml) at 12 mo

George et al. . JID 2007;195:1411-8

National Statistics: Uganda



- HIV prevalence: 6.4%
- Estimated number of HIV infected: 950,000
 - Paediatric HIV/AIDS patients: 140,000
- Total number requiring ART: 208,000
 - 43,700 (21%) requiring ART are children
- Number on ART: 100,000 (Apr07)
 - **Children account for 10% of the 100,000**
 - **Only 20 % of eligible children are on ART**
 - **Mulago contributes 22% of all on ART**

Uganda



- Makerere University, Mulago Hospital, Kampala Uganda
- 250 children
 - Median age 9.2 years
- 74% undetectable (< 400c/ml) at 1 year

Kamya, JAIDS 2007 46(2):187-93

Children with HIV and Malaria Project (CHAMP)



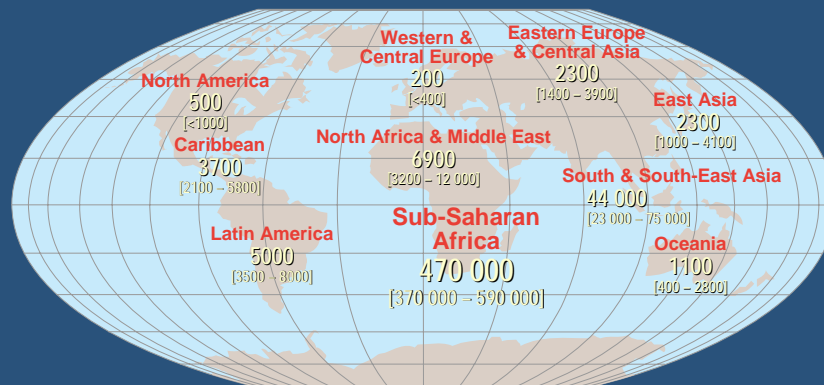
- Very well resourced clinic with aggressive follow up, Kampala Uganda
- Observational cohort of 300 HIV infected children enrolled at age 1-10 yrs
- 78 started ART on study
- 86% undetectable (< 400 c/ml) at 6mo
- 75% undetectable at 12 months

Future Directions

- Push for Early diagnosis
 - HIGH infant mortality
 - DBS based community testing
- Aggressive OI prophylaxis
- Increased access to ART
- Adherence programs
- More Treatment options (drug and formulation)
- More data
 - Timing - When to start, when to switch
 - Resistance and second line therapy



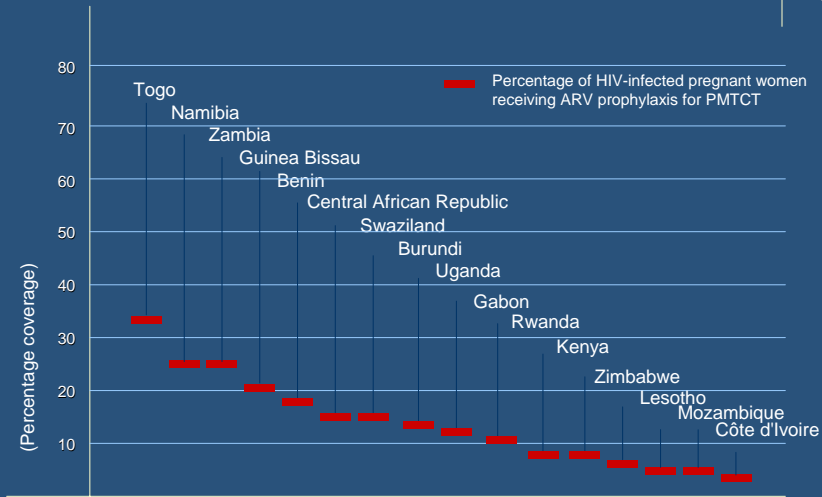
Children (<15 years) newly infected with HIV in 2005



Total: 540 000 (420 000 – 670 000)

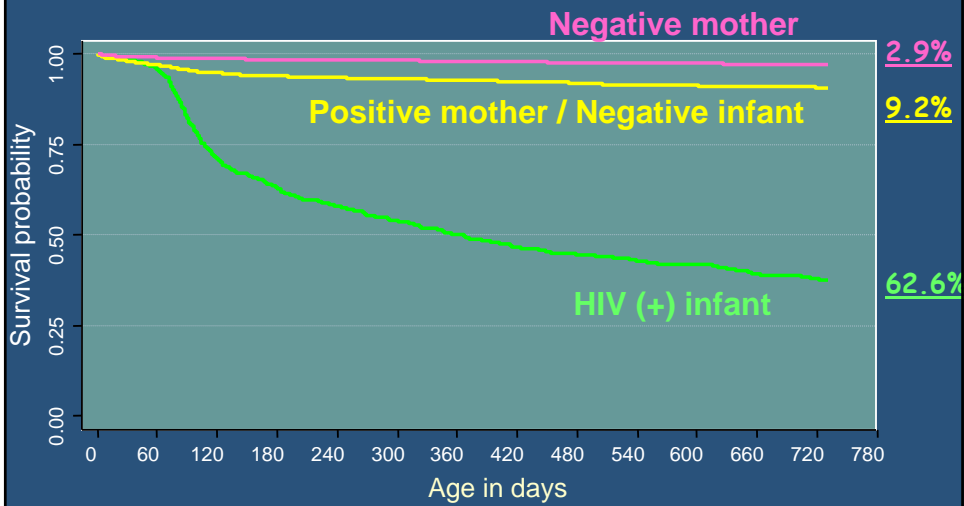


Access to PMTCT services in sub-Saharan Africa, 2005



UNAIDS, 2006

Mortality from birth to 24 mo.



PIDJ, 2007; 26: 519-526.

Call for Prevention



- Expand access to PMTCT for mothers
- Expand access to TREATMENT for mothers
- Higher goal – complete suppression
 - Lower transmission rates
 - Intrauterine
 - Peripartum
 - Breast milk
 - Improve health of their infants HIV (-) and (+)

Acknowledgement



- Philippa Musoke (Makerere University, Kampala)
- Annette Sohn (UCSF)
- Jean Humphrey (Zvitambo)
- CDC
- WHO



Web Resources

- www.who.int/hiv/pub/guidelines/art/en/index.html
 - Pediatric guidelines per WHO
- www.aidsinfo.nih.gov/Guidelines
 - Pediatric Guidelines per NIH
- hivinsite.ucsf.edu



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