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Mother-to-child HIV Transmission

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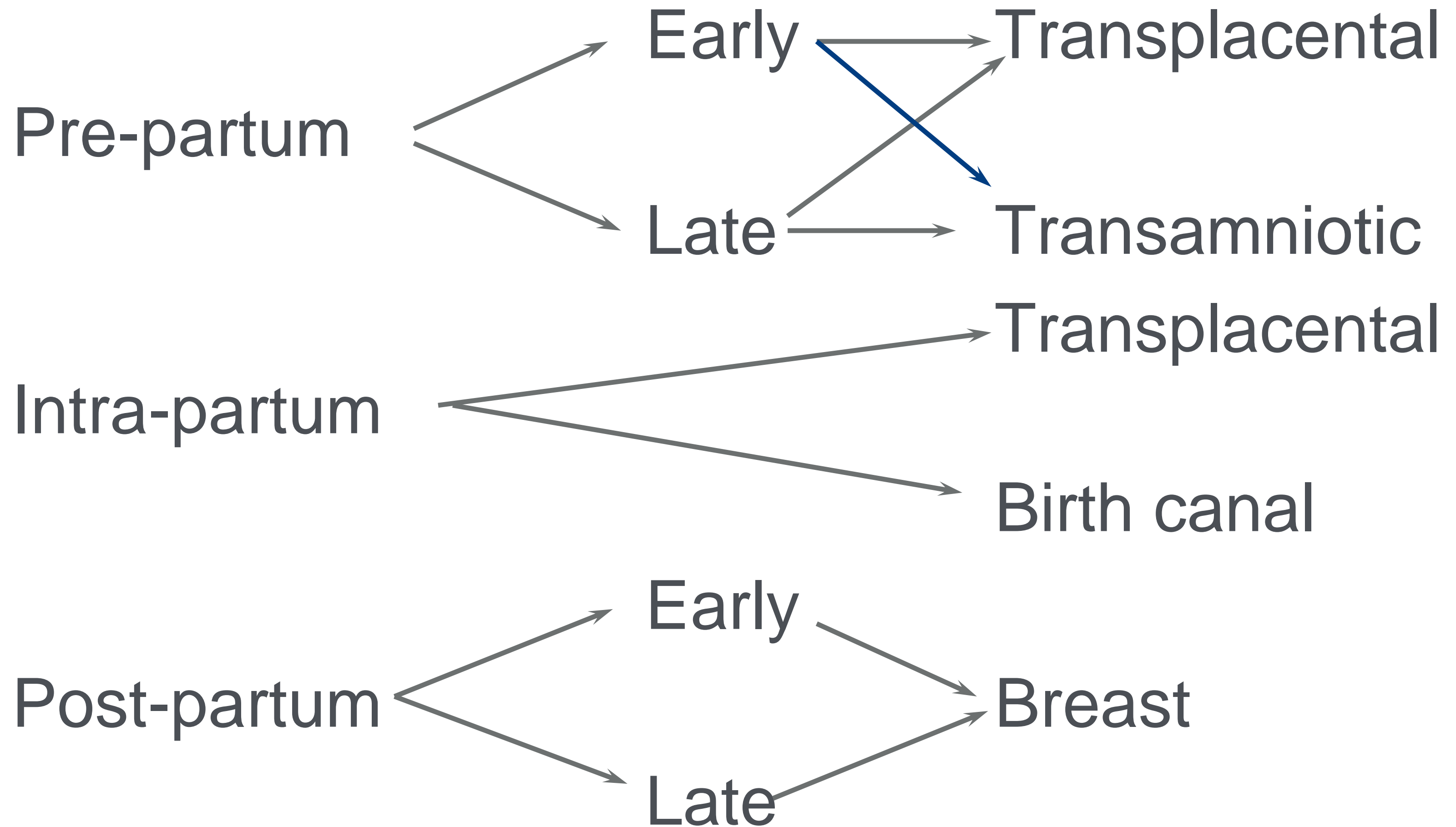
Where and when might HIV transmission occur?

The Time and the Place



Early Intra-uterine Transmission I

HIV can infect placenta at all stages.

AIDS 1997;10:711-715
J Virol 1991;65:2231-2236

Hofbauer cells +/- trophoblasts CD4+ and can be infected *in vitro.* Clin Inf Dis 1992;15:678-691

HIV-1 detected in fetal material as early as 12/52.

Lancet 1985 ii 1129
Lancet 1986 ii 288-9
AIDS 1995;9:359-366

HIV detected in amniotic fluid

Lancet 1987;ii:459-60

Chorioamnionitis associated with increased transmission JAMA 1993;269:2853-9

Early Intra-uterine Transmission II

Low frequency of HIV in fetuses AIDS 1995;9:359-366

The intact placenta is an efficient barrier and 1st and 2nd trimester transmission rare (?2%)

Supported by intervention data

Prevention would be difficult

(? importance of seroconversion, malaria)

Intra-partum Transmission I
Birth canal

HIV-1 is detected in cervico-vaginal secretions

JAIDS 1993;6:72-75, JID 1997;175:57-62

HIV is detected in neonatal gastric aspirates

JID 1996;173:1001-4

and oropharyngeal aspirates but less often if mother took ART

JID 1998;177:1097-100

Efficacy of vaginal cleansing with Chlorhexidene if ROM>4hr

Lancet 1996;347:1647-1650

Intra-partum Transmission II
Birth Canal

Higher rates of transmission are reported:

- First Born twin J Pediatr 1995;126:625-632
- Prolonged rupture of membranes
- Long Labour Am J Obstet Gynaecol 1996;175:661-7
- Haemorrhage during labour
- Bloody amniotic fluid JID 1996;173:1001-4
- Bloody neonatal gastric aspirate

Intra-partum Transmission - III Transplacental

Data from International Twin Registry

35% transmission 1st born vaginal delivered

8% transmission 2nd born Caesarian delivered

Suggests 1/3 transmission is intrauterine

J Pediatr 1995;126:625-632

Early, high viral load in some neonates

Infants with early HIV+ results CD8+ DR+ lys

J AIDS&HR 1997;15;204-210

Feto-maternal mixing of cells occurs

J Med Genetics 1975;12:230-242

Timing Perinatal Infection

Rouzioux's Model

Am J Epidem 1995;142:1330-7

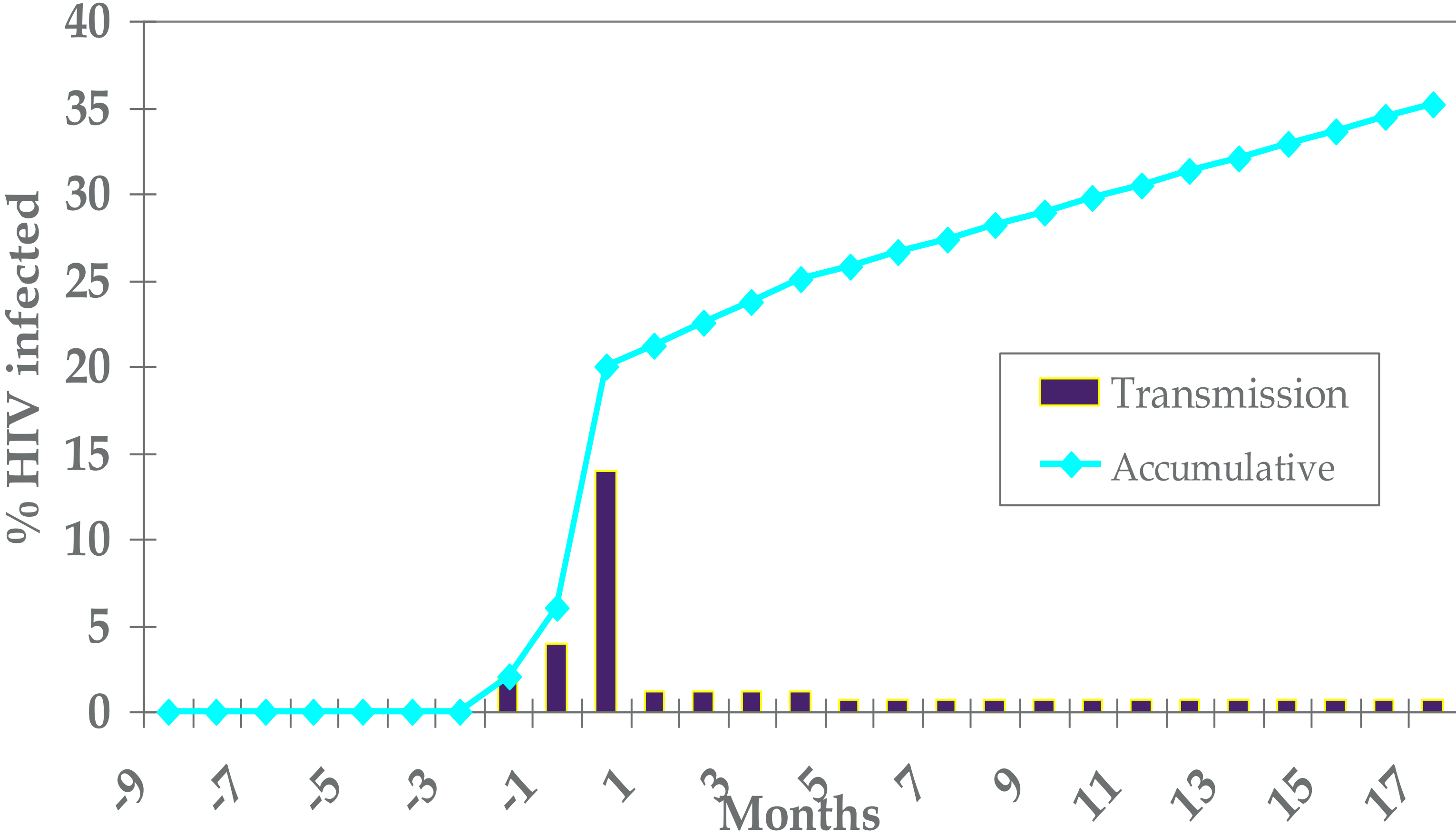
Studied 95 HIV infected infants:

- 17% +ve at birth
- 50% +ve by 10 days
- 95% +ve by 2 months

Used appearance of new positives to conclude:

- <2% infected > 2 months pre-partum
- 35% infected < 2 months pre-partum
- 65% infected on the day of delivery

Mother-to-child transmission of HIV-1 in a Breast-feeding population



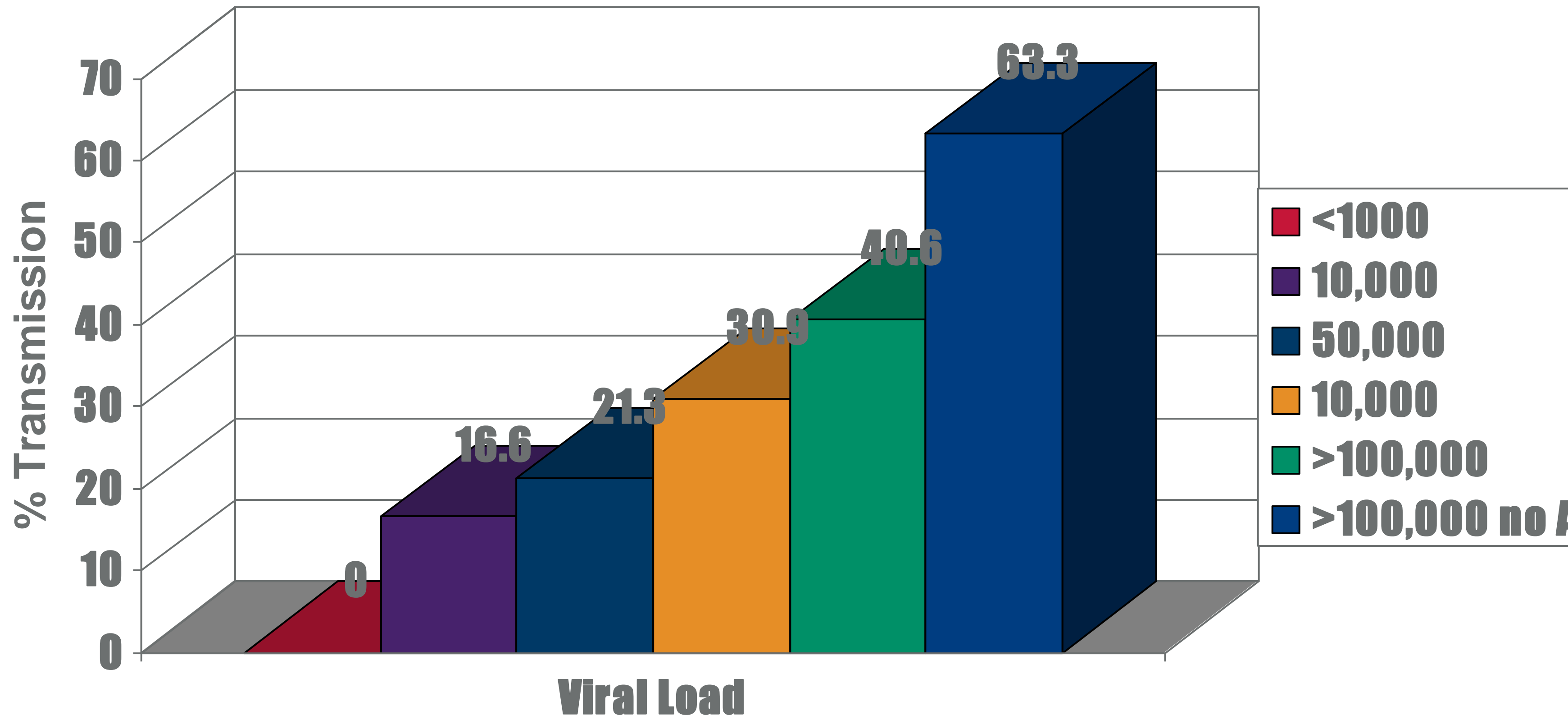
What factors might influence HIV Mother-to-child Transmission?

Factors influencing Transmission

Maternal CD4 lymphocyte count
Maternal Viral Load
Vitamins
Chorioamnionitis
Pre-term Labour, Low Birth Wt
Amniocentesis
Duration of Rupture of Membranes
Order of birth if Twin
Neonatal CCR-5 genotype
Gender
HIV infection acquired during gestation?
HSV ?
Malaria ?

HIV RNA load and Transmission

Garcia et al, NEJM 1999;341:394-402



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Prevention of HIV infection in Non-BF Populations

477 women (USA, France) CD4 >200×10^6/L

Zidovudine 100mg x 5/day 2nd Trimester
Zidovudine 1mg/kg/hr IVI during labour
Zidovudine 2mg/kg/6hr po neonate 6/52

HIV transmission - Placebo **25.5%**
- Zidovudine **8.3%**

67.5% relative reduction in transmission

NEJM 331: 1173-80 3.11.94

Zidovudine Thai Study

Double-blind placebo controlled of 397 women

Zidovudine 300mg bd from 36 weeks (25 days)

ZDV 300mg every 3 hrs during labour (3 doses)

Formula feeding but no neonatal component

Median $CD4^+$ 424/μl (at enrollment)

14% delivered by Caesarian section

ZDV 17/193 (9.2%) v Placebo 35/198 (18.6%)

51% reduction in transmission (p 0.008)

MMWR 1998;47:151-3

Prevention of HIV infection in Breast Feeding Population: DITRAME TRIAL

421 mothers, 400 infants 9/95 - 2/98

36 weeks to 1 week post partum

Median CD4 545/ml

Zidovudine 300mg bd v placebo

74 - 79% breast feeding @ 6/12

Paediatric HIV diagnosis by *gag* & *pol* PCR

Dabis et al, Lancet 1999;353:786-792

Abidjan Study:

Rate of HIV-1 in population 12.7%

280 mothers 8/96 - 2/98

94% CD4 >200/μl

36/40 Zidovudine 300mg bd v placebo

Breast feeding population

98% children still breast feeding at 3/12

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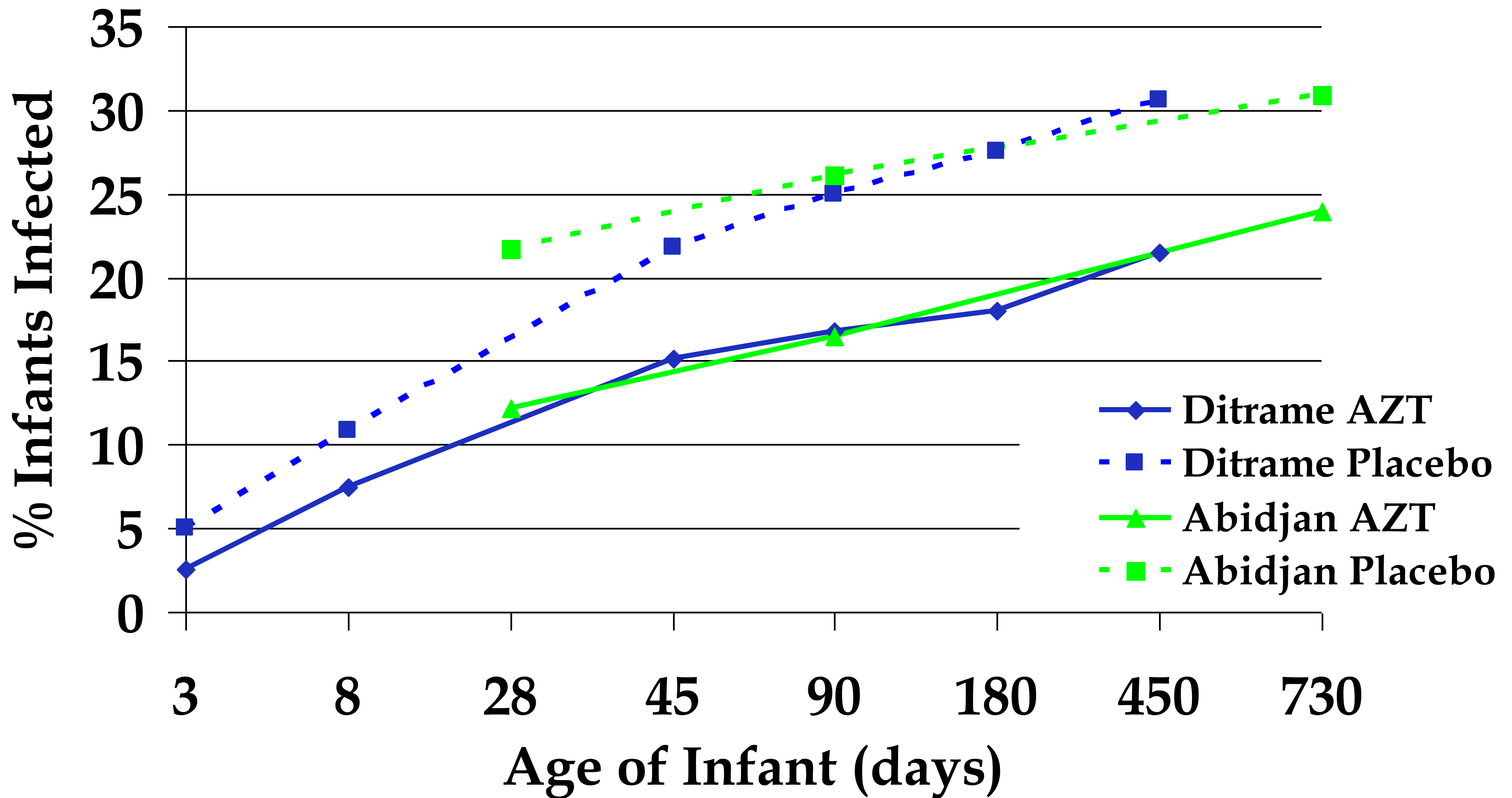
Abidjan Results

	Transmission %			
	Zidovudine	Placebo	Reduction	p
4/52	12.2	21.7	44%	0.05
3/12	16.5	26.1	37%	0.07
Deaths 2-120 days	2 (1.4%)	12 (8.8%)		<0.01

Wiktor et al Lancet 1999;353:781-785

The benefits of Short duration peri-natal Zidovudine are reduced but not eliminated by breast-feeding



HIVNET 012: Kampala 1997 - 1999

Single dose **Nevirapine 200mg** at onset of labour plus 2mg/kg to neonates within 72 hours of birth **v** **Zidovudine 600mg** stat then 300mg 3 hourly during labour plus 4mg/kg b.d to neonates for one week

	% infants HIV positive			
Age (mo)	Birth	2	4	18
Zidovudine	10.3	20.0	22.1	25.8
Nevirapine	8.1	11.8	13.5	15.7
P	0.35	0.006	0.006	0.002

41% Reduction in HIV Transmission

Brooks Jackson et al Lancet 2003;362:859-868

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ZDVm + SD Nevirapine

1844 mothers

Zidovudine in 3rd Trimester (36/40) – all

Randomised: Placebo - Placebo

Maternal nevirapine – placebo

Maternal & Infant Nevirapine

Transmission	Interim Analysis	Final
Placebo – Placebo	6.3%	
Maternal nevirapine – placebo	2.1%	2.8%
Maternal & Infant Nevirapine	1.1%	2.0%
	p 0.0026	p 0.03

M. Lallement et al NEJM 2004

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Efficacy of PLCS + ZDVm

436 women randomly assigned to ECS or SVD

1993 – Mar 1998 - Analysis Nov 1998 - 370 infants

Assigned to	n	Pos	%	
ECS	170	3	1.8	}
SVD	200	20	10.5	}p<0.001

Allocated MOD	No ZDV	ZDVm	
SVD	**19.5%**	4.3%	
ECS	3.9%	**0.8%**	(1/119)
% Reduction	80%	82%	

DITRAME: Results

	Transmission %			
	AZT	Placebo	Reduction	
Day 3	2.6	5.0	48	
8	7.5	10.8	31	
45	15.1	21.8	31	
90	16.8	25.0	33	
180	18.0	27.5	35	p 0.027

Dabis et al, Lancet 1999;353:786-792

HAART: WITS

WITS, n = 1542, 1990-2000, no BF, singleton live births

	<400	.4-3.5K	3.5-10K	10-30K	>30K
Tx	1%	5.3%	9.3%	14.7%	23.4%

2.4 fold increase Tx with 1log increase V/L at delivery

	no ART	ZDV	Combo	"HAART"
Tx	20%	10.4%	3.8%	1.2%
N =	396	710	186	250

2 transmissions at <400

HAART for 1 month pre delivery, illicit drug use throughout pregnancy

Combo RX, DROM > 24hrs

Cooper et al; JAIDS 2002;29:484-94

Very low risk of MTCT with interventions: UK & Ireland

Data 2000 – 2006 n = 5136 infants

Managed according to BHIVA guidelines (hopefully?)

Transmission

- 1.1% overall
- 0.8% if maternal ART >14 days
- 0.1% if HAART and VL <50 (3/2202)
- 0% if ZDVm + PLCS   (0/467) 95% CI 0.8%

Townsend et al, AIDS 2008

Very low risk of MTCT with interventions: UK & Ireland

Data 2000 – 2006 n = 5136 infants

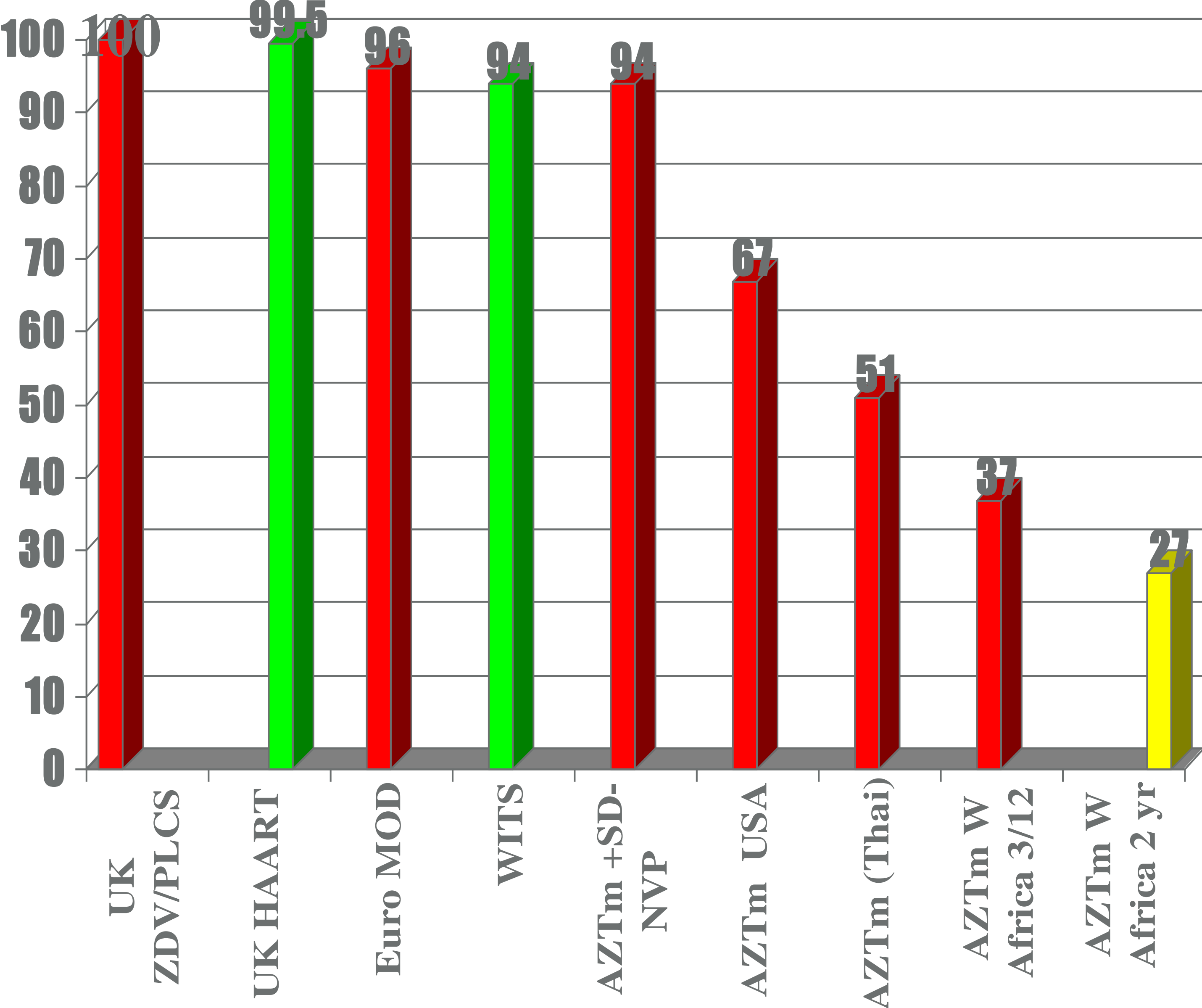
Managed according to BHIVA guidelines

Transmission

- 0.7% if HAART + PLCS (17/2337)
- 0.7% if HAART + SVD (4/565)

Townsend et al, AIDS 2008

% Reduction in MTCT with ART



Further Reading

The British HIV Association guidelines on Management of HIV infection in Pregnancy 2012 are an up to date resource both on the recommendations and their evidence base.

http://www.bhiva.org/PregnantWomen2012.aspx

Shapiro's paper on HAART during pregnancy and Breastfeeding provides the data to support the current WHO recommendations for women living in resource limited settings – namely HAART during pregnancy and for 12 months whilst breastfeeding.

Antiretroviral Regimens in Pregnancy and Breast-Feeding in Botswana, Shapiro et al. NEJM 2010; 363:2282-2294

http://www.nejm.org/doi/pdf/10.1056/NEJMoa0907736