

Future Directions for HIV Vaccine research in HIV prevalence developing country settings

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**If you want to see
AIDS stopped in its tracks,
learn about HIV vaccine research.
You can't get HIV/AIDS from this vaccine.**

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Looking forward to a better future



HIV-vaccine trial to involve thousands in SA

South Africans of different races, sexual orientation and economic status are being recruited for \$35m experiment

Tamar Kahn

Science and Health Editor

CAPE TOWN — Scientists have begun recruiting South African volunteers to test pharmaceutical giant Merck's candidate HIV vaccine in the largest and most advanced study of its kind to take place in SA to date.

It is being run in parallel with another trial in the US and Latin America, and will help determine whether the jab works against different strains of the virus, including the C-strain common to this region.

SA plays a pivotal role in global HIV research because it has strong scientific capacity and a high

prevalence of the disease. At least 5.5-million South Africans, or 11% of the population, are infected with the virus.

"A vaccine would be the ultimate protection against HIV, hopefully for the duration of (one's) reproductive life," said the trial's principal investigator, Glenda Gray, of the perinatal HIV Research Unit at the University of the Witwatersrand.

Merck's candidate vaccine, MRKA5 HIV-1, is based on a modified version of the common cold virus combined with three HIV genes. It has already been tested for safety in phase I and IIa trials, and scientists are now assessing whether it stimulates the body to

recognise and kill HIV that invades the body, and if so, whether it is equally effective against different strains of the virus.

The candidate vaccine was developed against the clade B virus, but scientists hope it will also help people defend themselves against clade C, the strain most common in sub-Saharan Africa.

The \$35m trial, dubbed Phambili, is being run by the international HIV Trials Network and the South African AIDS Vaccine Initiative, with backing from Eskom and the South African government. It has been approved by the US Food and Drug Administration, the South African Medicines Control Council and the

agriculture department, and will be overseen by an independent monitoring board.

News of the HIV vaccine trial comes barely a week after US-based health research group Conrad halted studies of UsherCell, a gel containing a cotton-based compound called cellulose sulphate, after interim analysis of trial data from more than 1 300 women in SA, Benin, Uganda and India showed more HIV infections among women using the microbicide than those given a dummy gel.

Independent monitors found that 22 of the 34 women who had used the gel and become infected were from SA.

The South African arm of the Conrad HIV microbicide trial was headed by the Medical Research Council's (MRC's) Prof Gita Ramjee, and funded by the US Agency for International Development and the Bill and Melinda Gates Foundation. According to the MRC, 11 previous studies of the gel had not identified any problems.

Gray said researchers had been worried about public perceptions of the risks involved in HIV research, but having alerted journalists to the launch several weeks ago, had decided to go ahead as planned.

"It's a terrible time to launch ... but if we didn't announce it today, people might have thought we had

something to hide," she said. Gray said it was inevitable that some test products would fail, and so all the HIV vaccine trials under way in SA offered treatment to people who became infected.

Scientists have already recruited the first 16 volunteers for the HIV vaccine trial, which aims to enrol 3 000 people of different races, sexual orientation, and economic backgrounds in four provinces — Gauteng, North West, Western Cape and KwaZulu-Natal. Participants will be given free male and female condoms, and advice about safe sex. Men will also be offered circumcision, which research shows reduces the risk of HIV transmission.

**PERINATAL HIV
RESEARCH UNIT**

**Future Vaccine Research will
need to Focus on**

Young Women

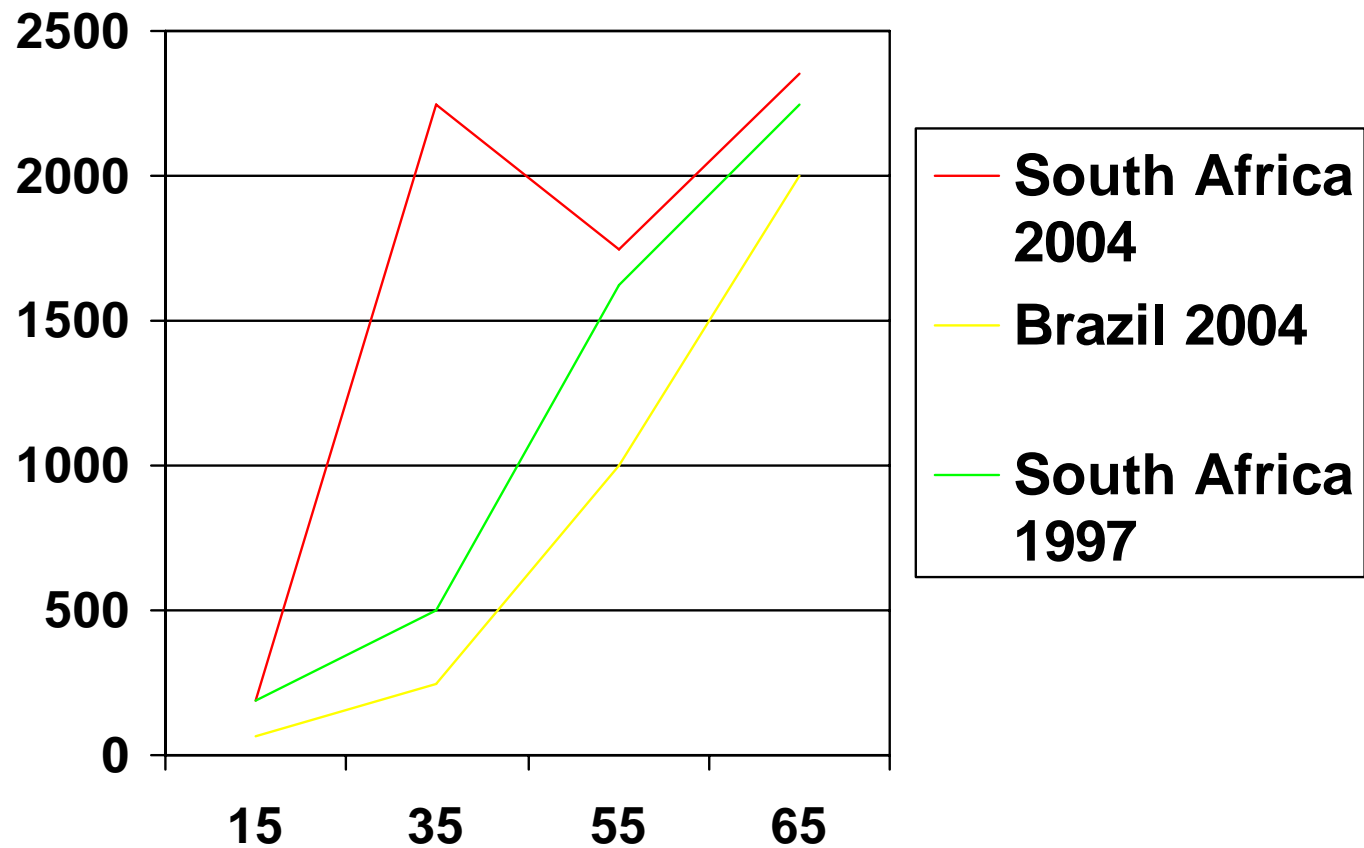
Infants

Human Capital

Human Capital

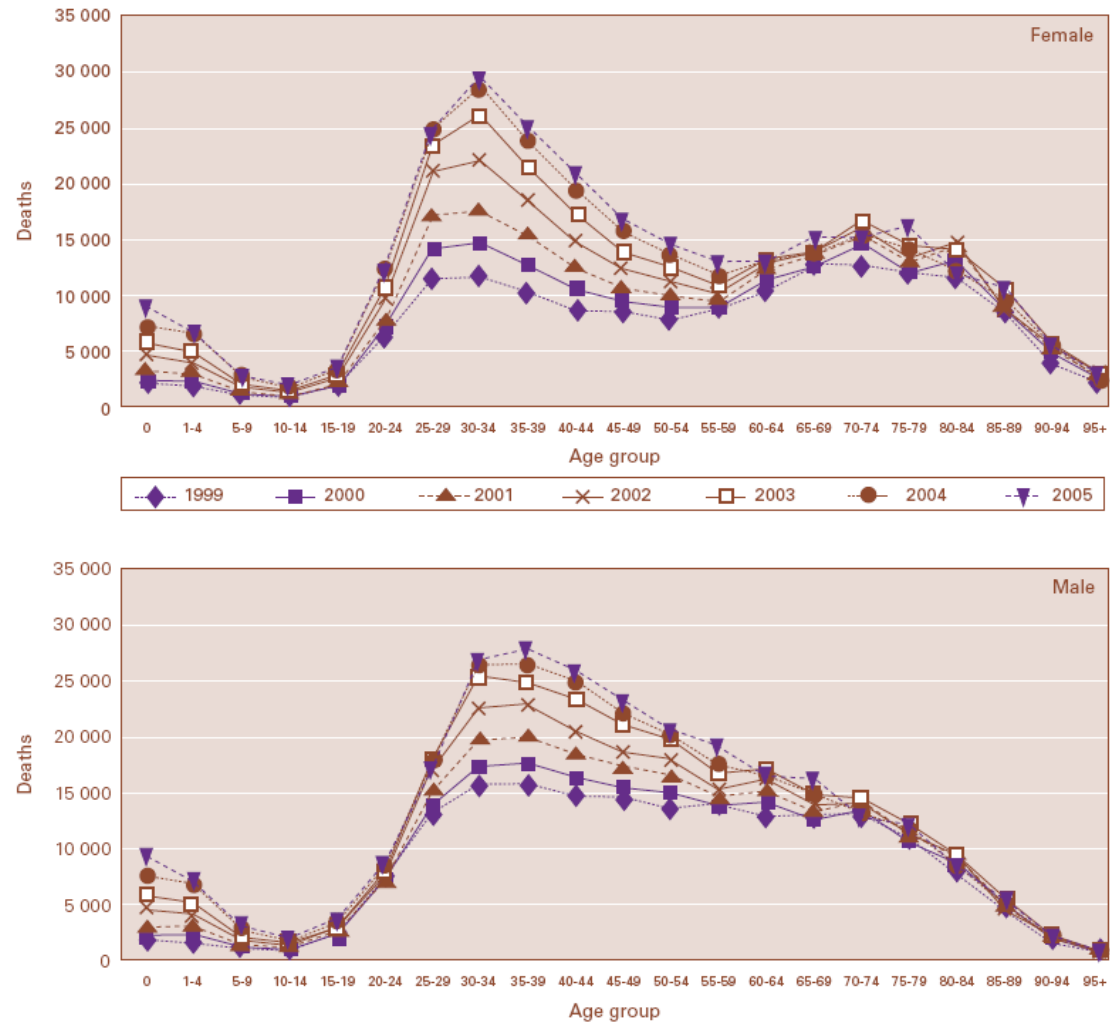
Setting	Researcher/million inhabitants
Developed World	3272/1000 000
Developing World	374/1000 000
Least-developed Countries	4.5/1000 000

Recorded female deaths in South Africa and Brazil per 1000, 000



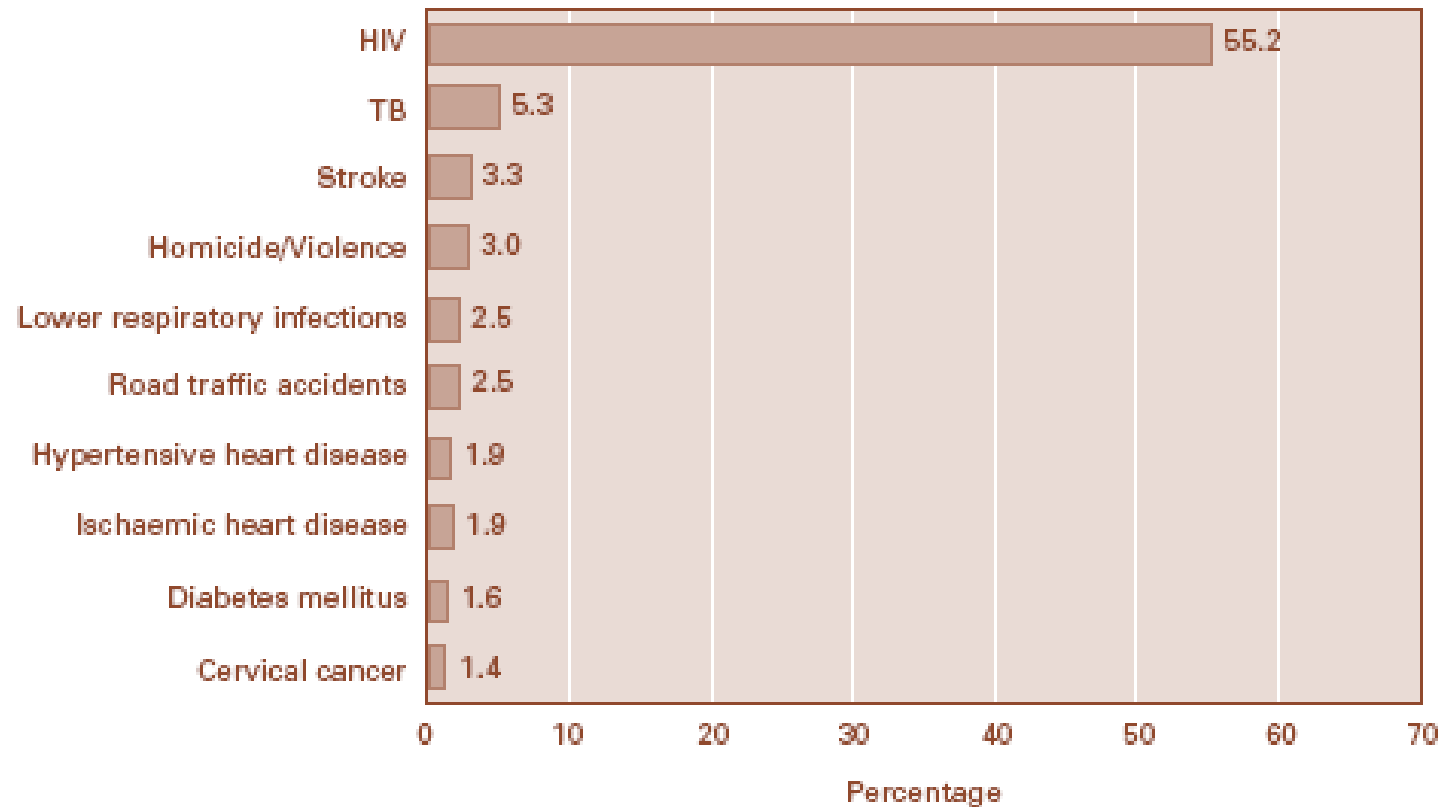
Source: Statistics SA; Instituto Brasileiro de Geografia e Estatística

FIGURE 1:
Trend in deaths on the population register by sex, 1999-2005



Source: Bradshaw D, data from Department of Home Affairs.

FIGURE 11:
Leading ten causes of death nationally for women 15-54 years, 2000²⁶



Source: Bradshaw et al., 2005.²⁸

TABLE 1:

Increase in reported deaths in children <15 years of age in South Africa 1997-2004

Year of Death	Reported Deaths
1997	38 194
1998	44 169
1999	44 810
2000	45 861
2001	48 090
2002	54 101
2003	60 231
2004	66 072
Increase 1997-2004	72.9%

Source: Statistics South Africa.²⁰

Leading ten causes of death nationally and in each province for children under-5 years, 2000

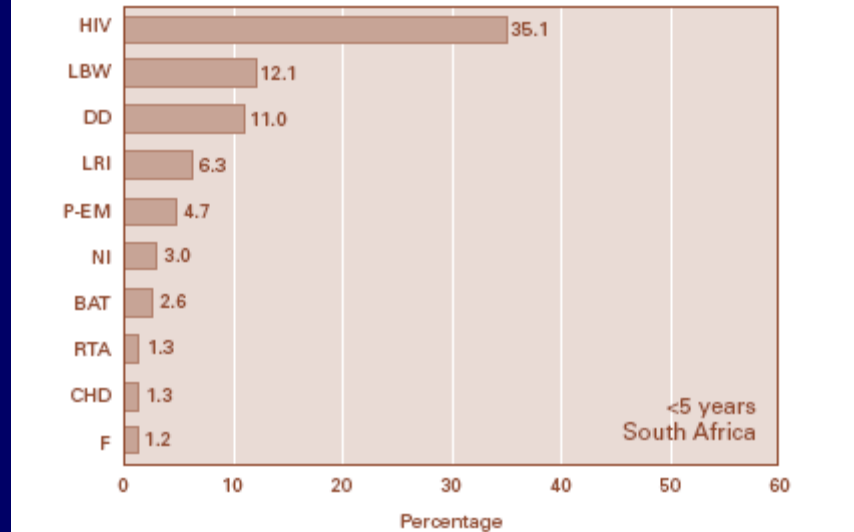
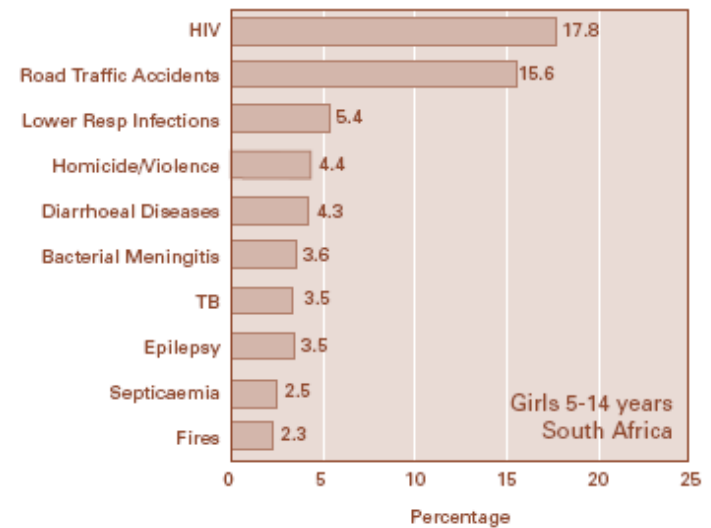
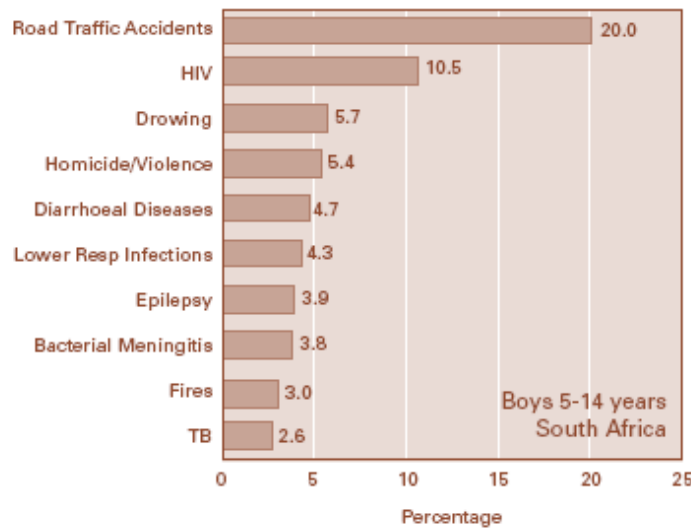
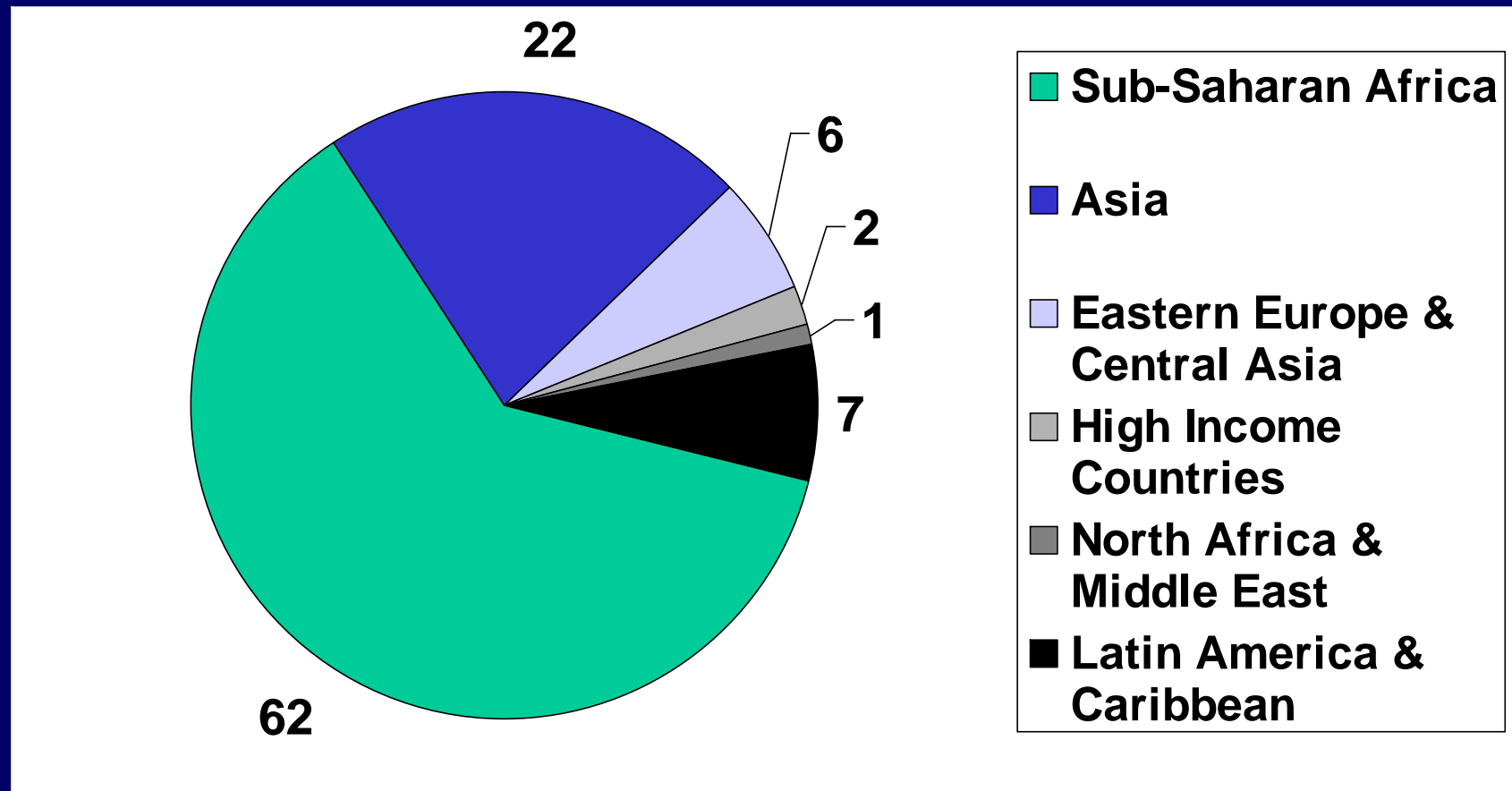


FIGURE 8:
Leading ten causes of death nationally for children 5-14 years, 2000



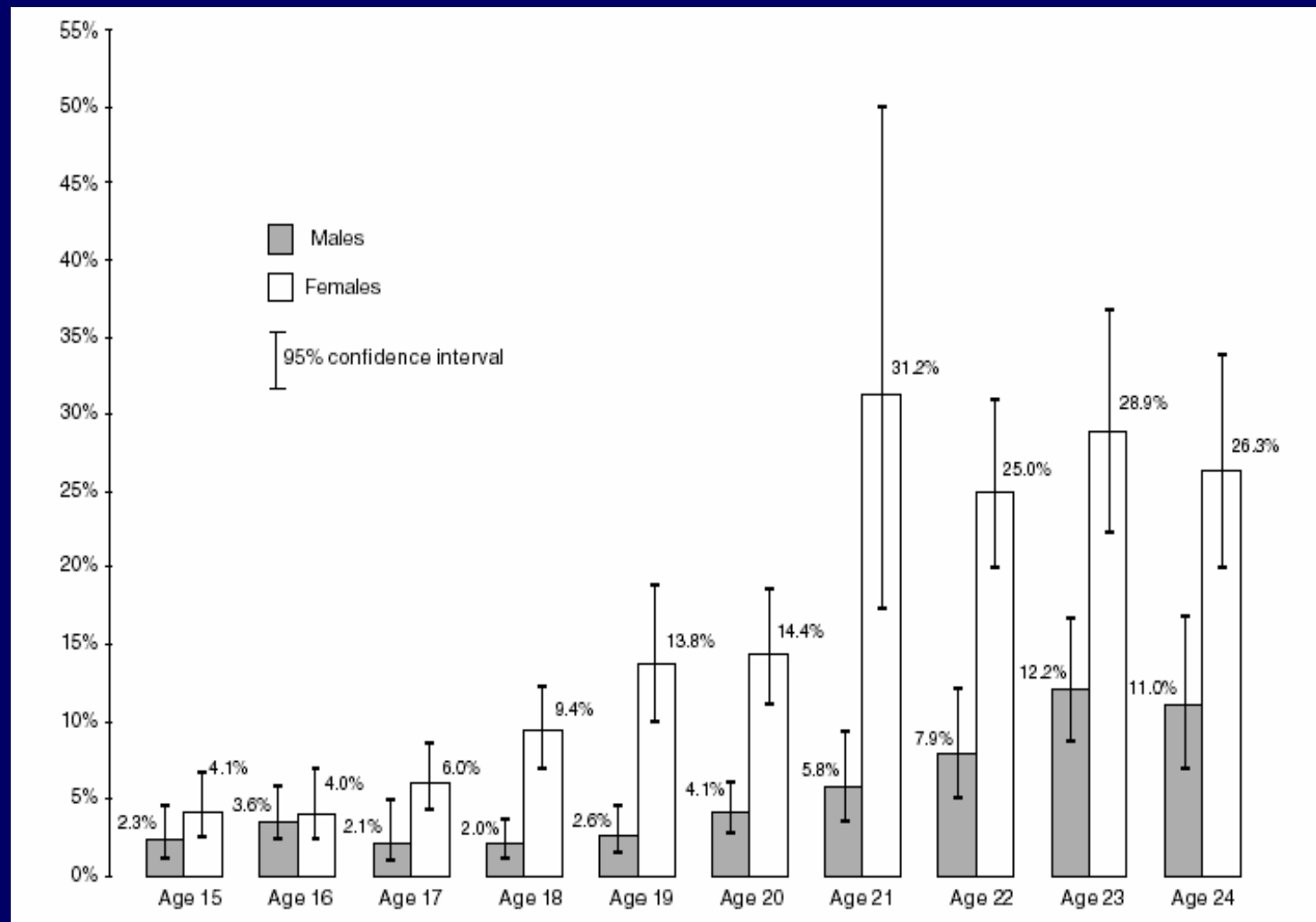
Region	Age Range	Proportion with sexual experience		Condom use at last sex	
		F	M	F	M
Sub-Saharan Africa Malawi , 2000 Uganda, 2000 Zambia, 2001 Zimbabwe, 1999	15-19	37% 33% 44% 14%	59% 34% 63% 29%	29% 50% 28% 37%	29% 49% 29% 58%
Eastern Europe Azerbaijan, 2001 Romania, 1999	15-19	<1% 22%	U 45%	47% 57%	U U
Asia Philippines, 2004	15-24	16%	31%	27%	22%
Latin America Brazil, 1996 El Salvador 2002-2003	15-19	22% 25%	63% 50%	U 50%	34% 62%
Developed countries Australia, 2001-2003 USA	16-19 15-19	56% 46%	59% 46%	54% 54%	80% 71%

Young people aged 15-24 years living with HIV



Joint United Nations Programme on
HIV/AIDS, 2004

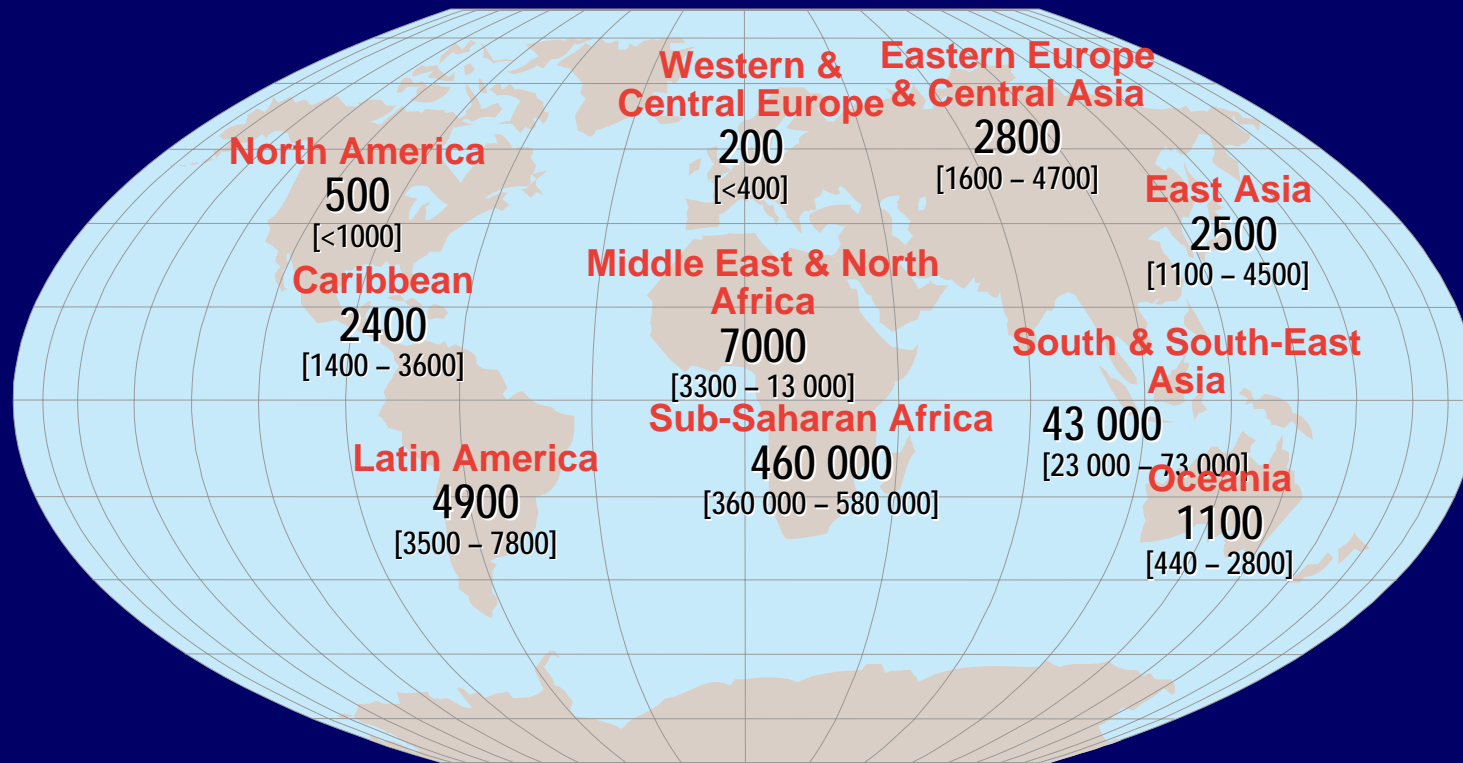
South African Youth Household Survey 2003: HIV prevalence (11 904 15-24 year olds)



IAS 2007: Female controlled technologies prevention studies

Study	No.	Active Arm HIV infections (Proportion of participants infected)	Control Arm HIV infections (Proportion of participants infected)	RR (95%CI)
Phase III CS (Conrad) Nigeria ^{Cates, IAS 2007}	2160 (ITT)	10 (1.8%)	13 (2.3%)	0.8 (0.3-1.9)
Phase III CS (Conrad) Multi site Africa ^{van Damme, IAS, 2007}	1428 (ITT)	25 (3.5%)	16 (2.3%)	1.61 (0.86-3.01)
	HIV infections per protocol	23 (3.3%)	11 (1.6%)	2.17 (1.06-4.45)
MIRA Diaphragm study ^{Padian, IAS, 2007}	4948	158 (6.4%)	151 (6.1%)	1.05 (0.84–1.32)

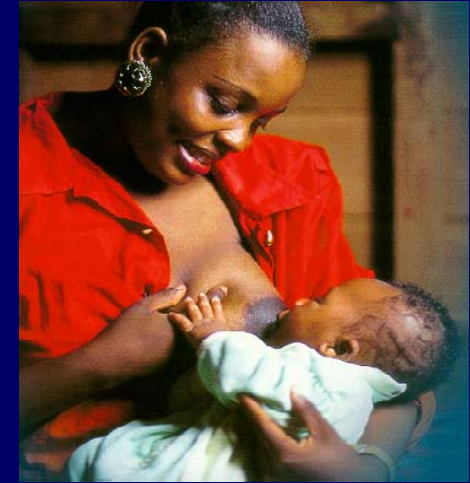
Estimated number of children (<15 years) newly infected with HIV, 2006



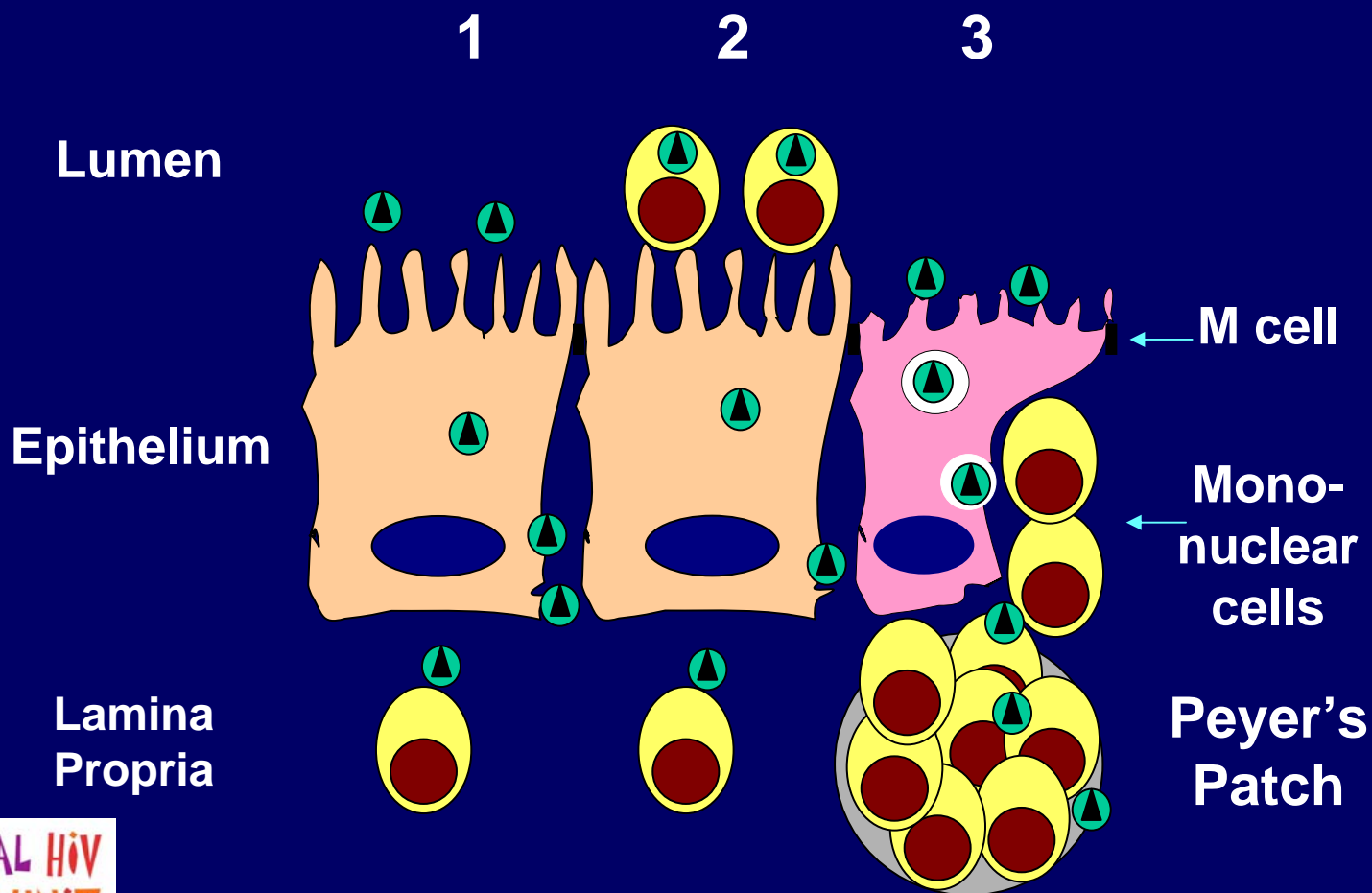
Total: 530 000 (410 000 – 660 000)

Breast milk Transmission

- Even with complete coverage of an effective peripartum ART intervention, *without an effective intervention to prevent breast milk transmission* an estimated **300,000** children will acquire infection through breastfeeding each year
- Preventing HIV transmission during the breastfeeding period remains a “vexing” challenge in places where infant formula cannot be safely provided.

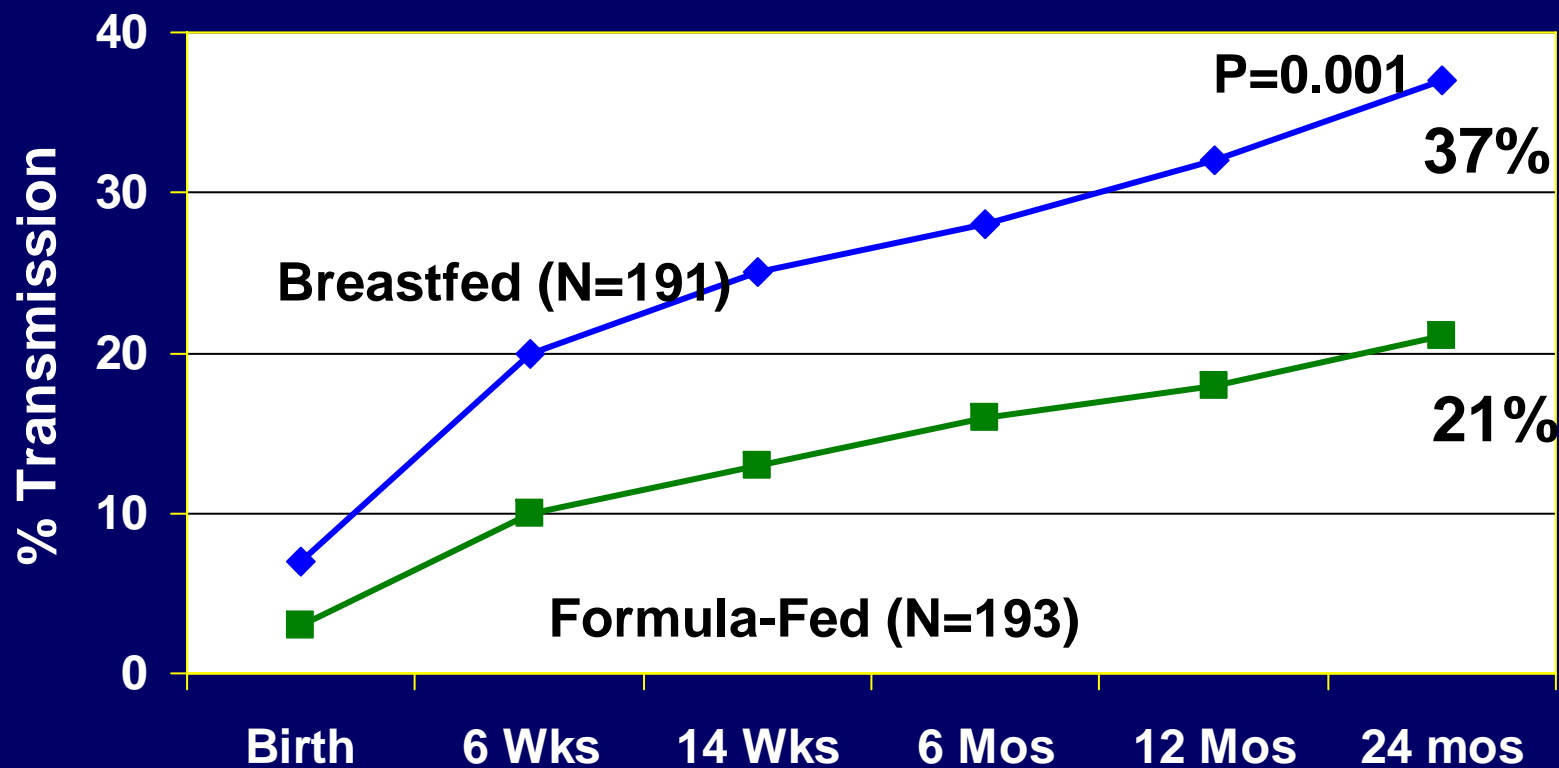


Potential Mechanisms of HIV-1 Transmission Through Intestinal Mucosa of Infant



Randomized Clinical Trial of Breastfeeding vs Formula-Feeding, Nairobi, Kenya

Nduati R, et al. JAMA 2000;283:1167-74

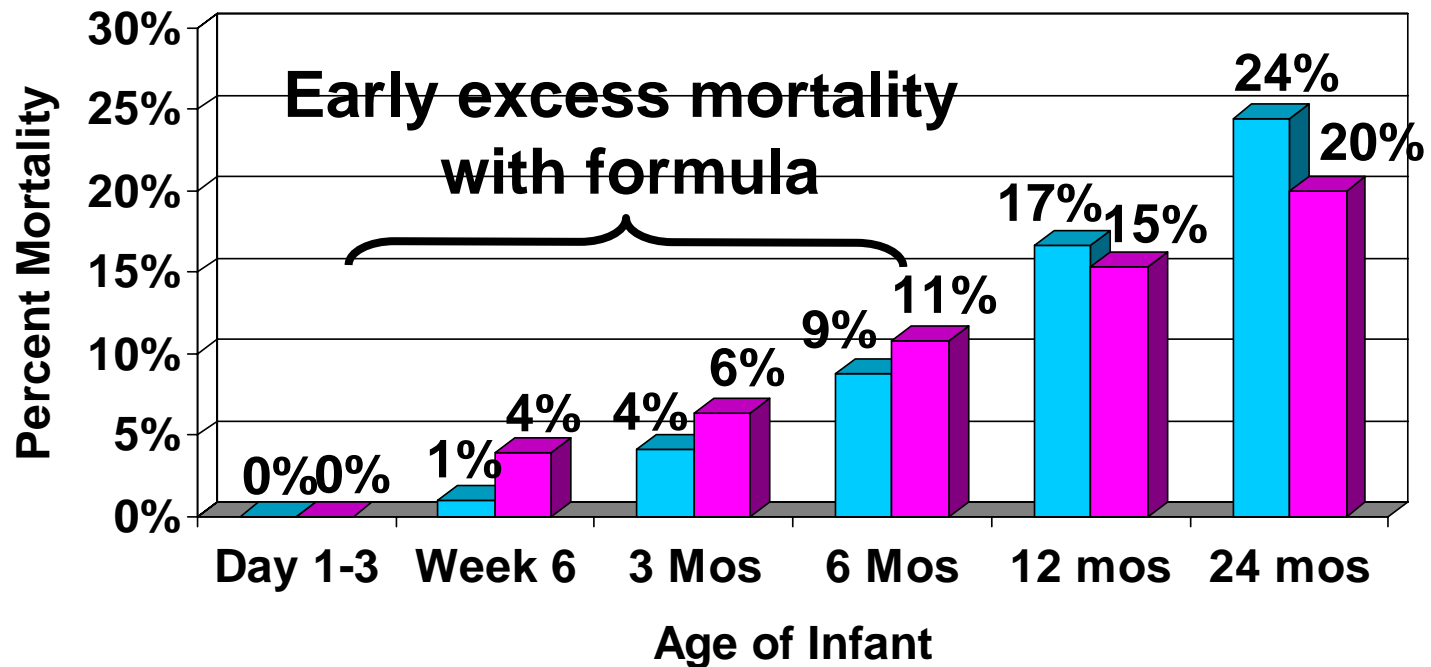


Overall rate of breast milk transmission was 16.2%;
75% of transmission occurred by 6 months

Higher Early Mortality in Formula-Fed Infants in Randomized Formula vs Breast-Feeding Trial, Kenya

Nduati R, et al. JAMA 2000;283:1167-74

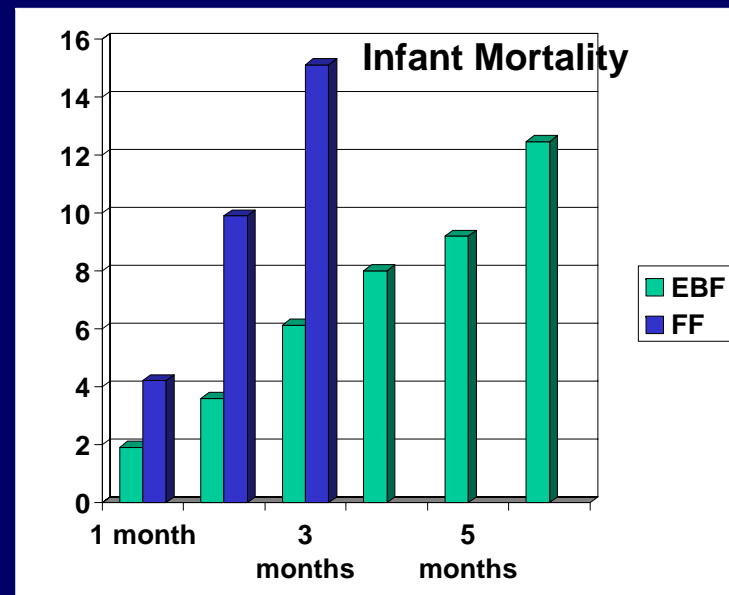
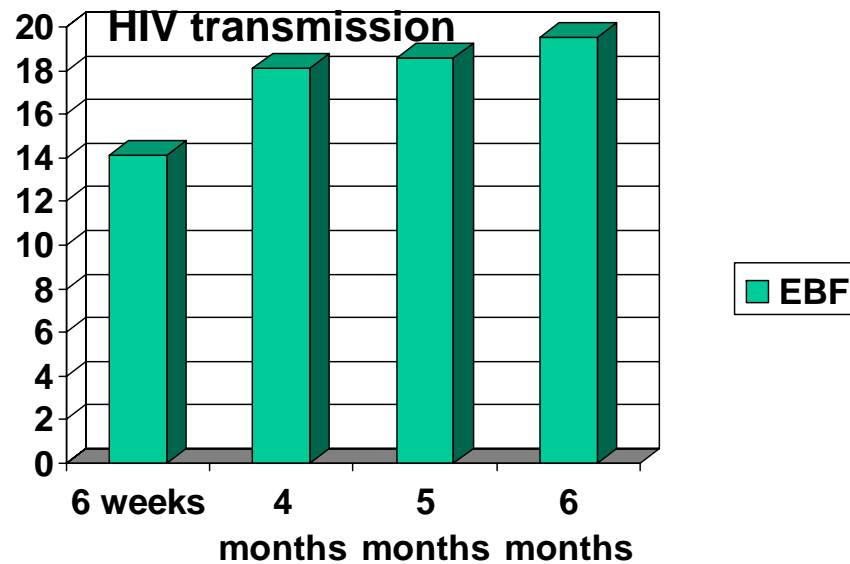
■ Breastfed infant mortality ■ Formula fed infant mortality



SAINT and Nairobi Trials: Early Differences in HIV Infection Rates in Breast- and Formula-Fed Infants

Nairobi	BF	FF	Diff BF-FF
Birth	7.0%	3.1%	3.9%
New infection 1-6 wk	12.9%	6.6%	6.3%
SAINT	BF	FF	Diff BF-FF
Birth	7.7%	6.6%	1.1%
New infection 2d-8wk	8.1%	2.5%	5.6%

Role of Exclusive Breastfeeding in HIV transmission, Coovadia H, et al, Lancet 2007

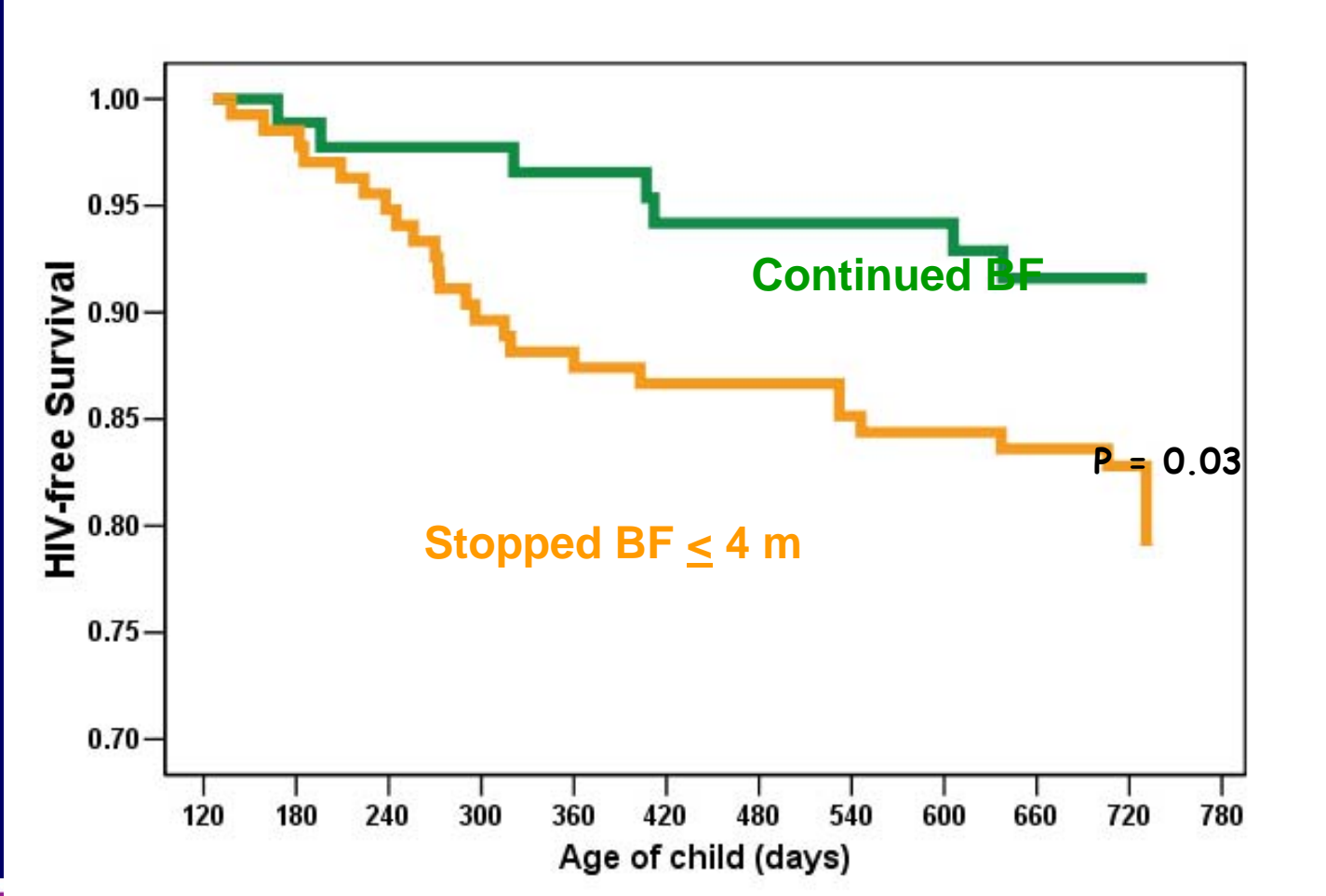


Multivariate analysis: Risk Factors for Infant Mortality

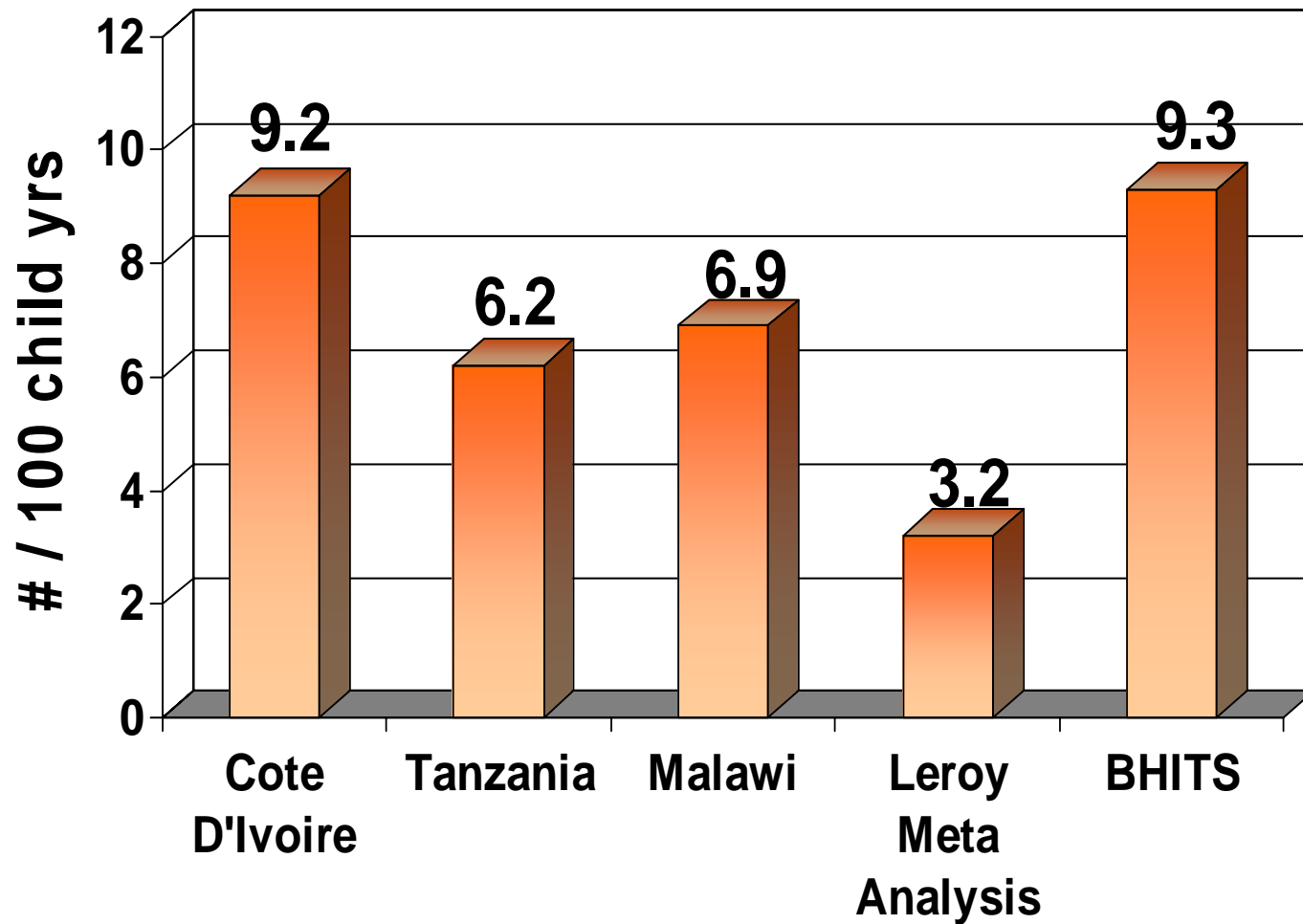
Infant feeding no effect

HIV infected babies were 15 times more likely to die than uninfected infants ($p < 0.0001$)

Among women not yet eligible for ARVs, stopping breastfeeding at 4 months (i.e. adherence with the intervention) was harmful - it increased the combined outcome of HIV infection or death, Kuhn L, et al, CROI, 2007



Overall Late (After Age 1 Month) Postnatal Transmission Rates in Different Studies



Rationale for HIV vaccines in PMTCT:

- Limited proven interventions available to reduce post-partum transmission of HIV through breastfeeding
- Protection is only needed for the duration of breastfeeding
- Global vaccine delivery systems are already set up for infants

HIV vaccine trials in HIV exposed infants

Name	phase	candidate	No.	schedule
HPTN 027 Uganda	I	vCP1521	50	4 doses over 3 months
PACTG 230 USA	I	rgp120	154	4 doses (0,4,12,20)
PACTG 326 First phase USA	I	ALVAC vCP205/vCP145 2 with or with out gp120	28	
PACTG 326 Second phase USA	I	vCP1452/vCP14 52 gp 120	30	

What should be the standard of care in HIV Vaccine breastmilk transmission trials?

- Minimize Infant deaths
- Minimize HIV transmission risk
- Adequate political and community involvement in trial designs

	MITRA PLUS (Maternal ARVS) Kilewo C, IAS 2007	MITRA (Infant PEP) Kilewo C, IAS, 2005	PETRA (no intervention) Lancet 2002
6/52 transmission rate	4.1%	3.8%	5.4%
6/12 transmission rate	5.0%	4.9%	11.9%

Human Capital Challenges in the developing world

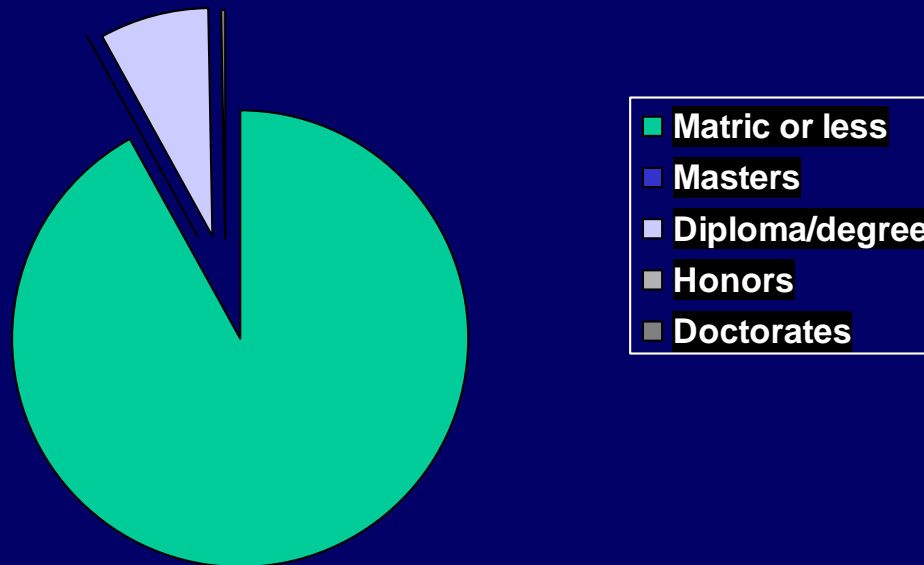
- Brain drain
- Brain circulation
- Brain gain

South Africa: Flight of the Flamingos: 1994-2000

Profession	Immigrants	Emigrants	Net gain/loss
Engineers/ architects	1 063	2 891	-2 667
Natural Science	489	1 482	-405
Medical Science	754	2 559	-2 072
Education and Humanities	1 805	5 547	-4 609
Legislature/ executive	2 564	5 070	-3 244
Total	6 675	17 549	-13 197

Lack of skill in RSA

- In 2001, only 8.4% of the total population over 20 years of age had tertiary education (Stats SA census, 2001)



Loss of Human Capital from Africa

- 40% of the African continent's top professionals live abroad
- 250 000 Nigerians live in the USA
- 23 000 qualified academic professionals emigrate each in search of better working conditions
- 1:4 Zimbabweans don't live in Zimbabwe (3.5m have left, 1.2m live in RSA, 1.1m in the UK)



Human Capital Challenges

- In Zambia 50/600 doctors trained since independence (1964) still reside in the country
- In Malawi, 28% of all nursing posts were filled in 2003
- 25% of all RSA doctors graduating 1990-97 are working abroad
- RSA: 32 000 nursing posts are vacant



Laboratory Capacity



Site Laboratory Challenges

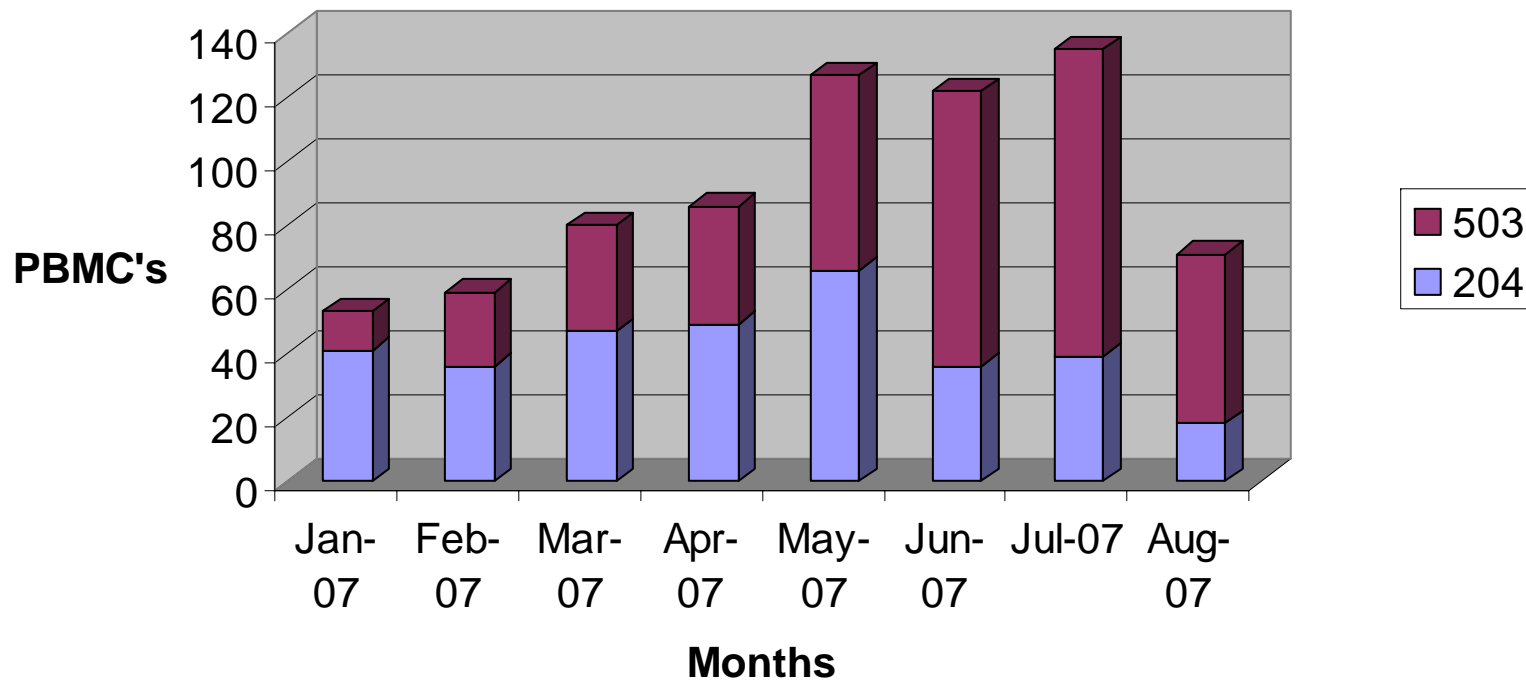
PBMC capacity

- Currently the rate limiting step in enrolling into phase IIb vaccine trials is PBMC capacity at the site
- Maximum capacity at current sites is sub-optimal



Site Laboratory Challenges: Soweto

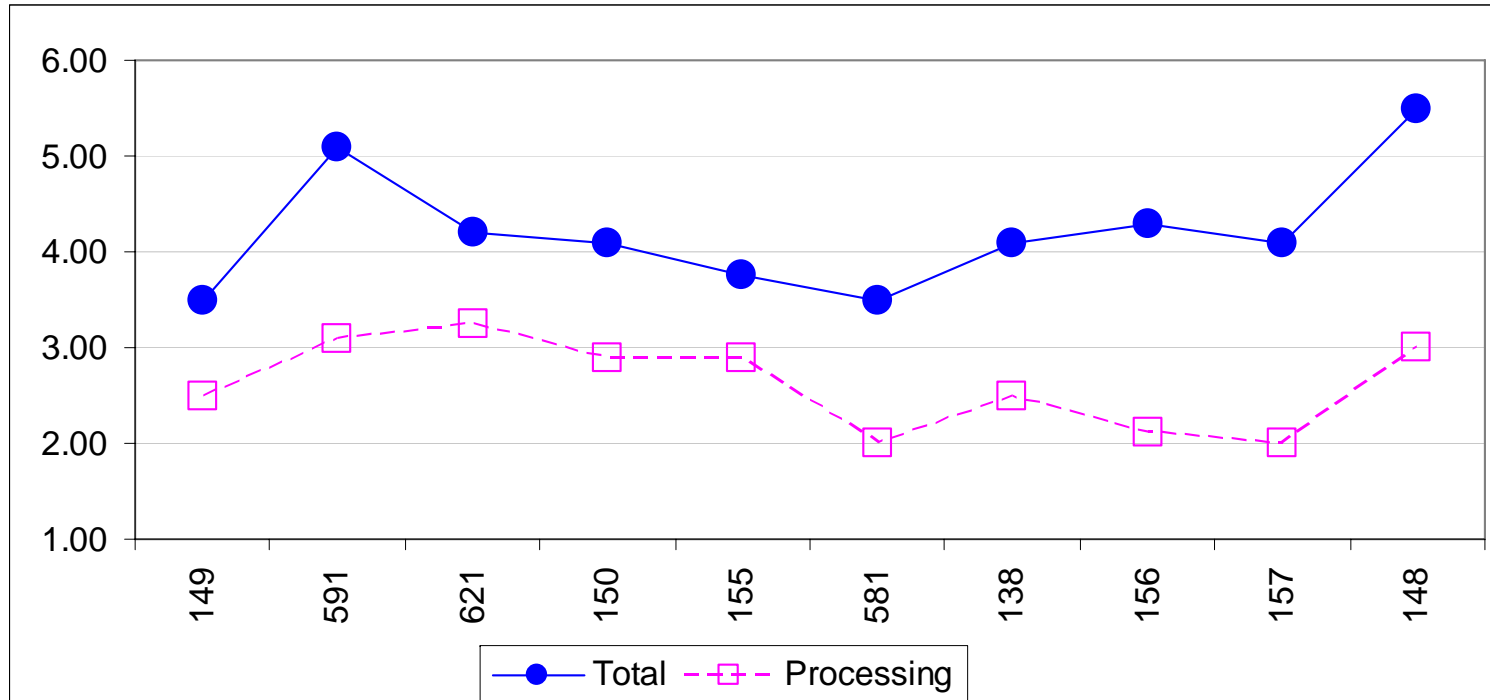
204 & 503 PBMC's



International PBMC Handling Times, 1Q07

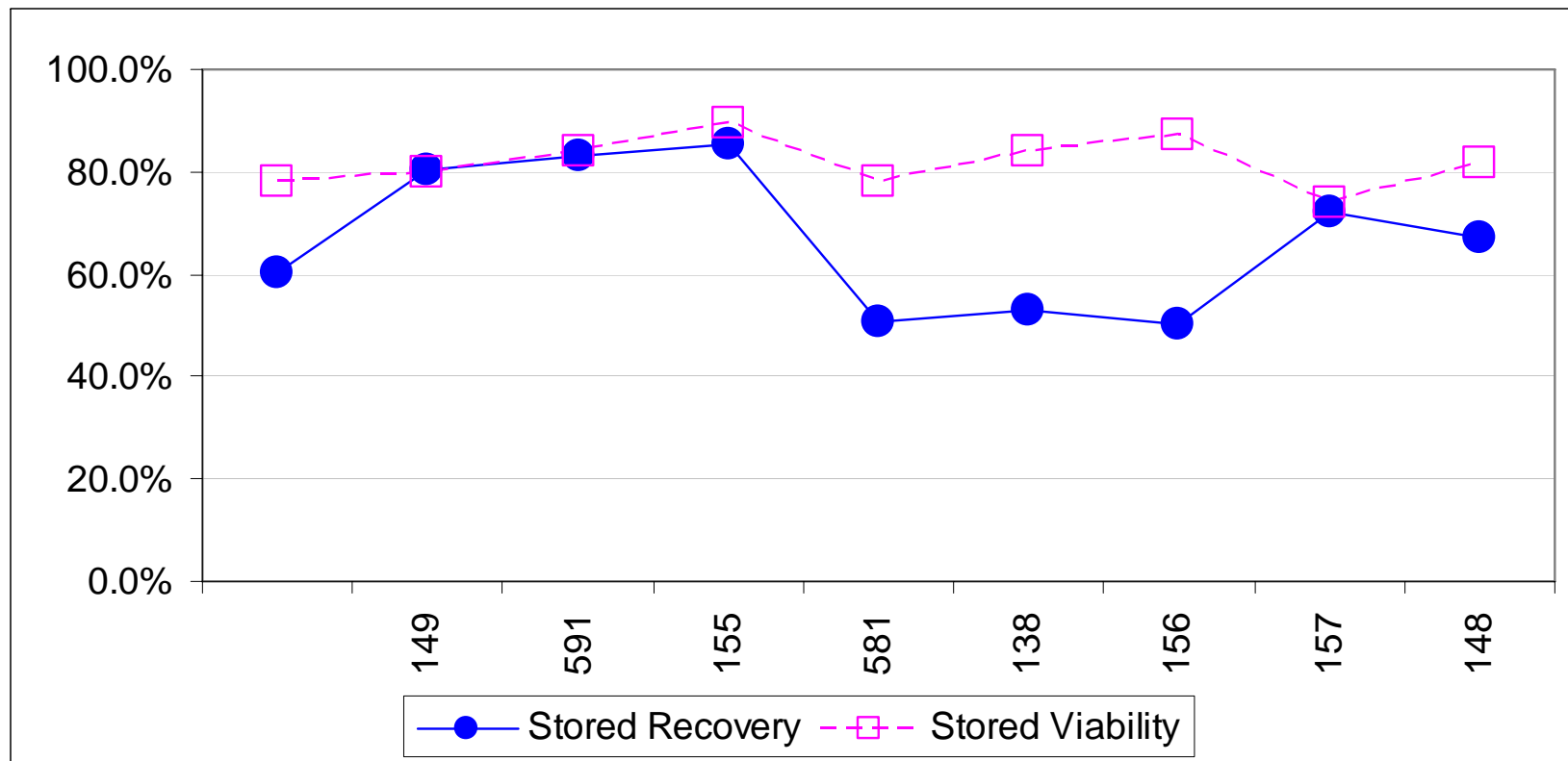
International Site Means

Total Time: 4.2 hrs / Processing Time: 2.6 hrs
(US site median: total 3.5 hrs, processing 2.6 hrs)



International PBMC EQC Summary 1Q07

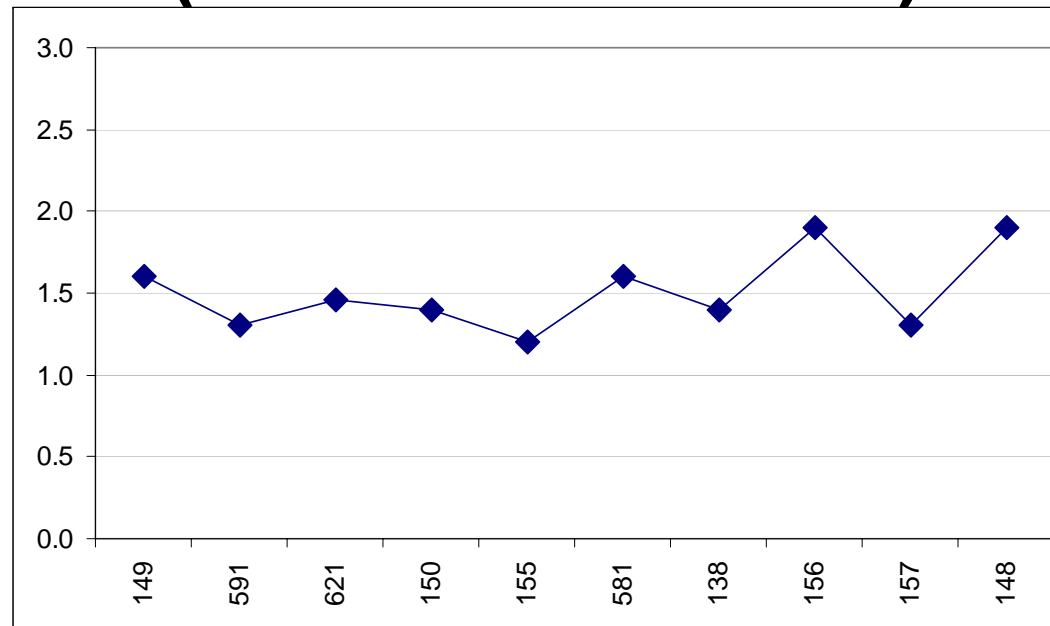
International Site Mean – Thawed Recovery: 67%
International Site Mean – Thawed Viability: 81.9%
(US site median: Recovery 71.7%, Viability 93.4%)



Average Cell Yield By International Site, 1Q07

International Site Mean

1.5×10^6 cells/mL of usable whole blood
(US site median 1.77)



Internal PBMC Quality Markers, Mar07

Sites	Cape Town	Soweto	Klerksdorp
Total Handling Time	4h 20m	4 hours	3h 30m
Total Processing Time	2 hours	2h 30m	1h 50m
Cell Yield cells x 10 ⁶ /mL	2.2	1.4	1.3

Stored PBMC Quality Markers, May7

Sites	Cape Town	Soweto	Klerksdorp
Mean Recovery Day 2 (>50%)	52%	65%	63%
Mean Viability Day 2 (>66%)	82%	86%	88%

South Africa PBMC Summary, Mar07

58% Tech Turn-Over	Difficult to build experience/expertise Lower cell yields, longer processing time Slow down or delay protocols Solution?
Cell Counting Cell Recovery	Re-training on manual cell counts/microscope Implementing automated cell counters (Jun07)
Cell Viability	Re-training on workflow, cold-chain, cell handling
Labeling	Re-training on LDMS and review process

Regulatory Challenges

- MCC: only one person at the administrative level at the MCC who oversees HIV vaccine trials
- Investigators: few investigators have the capacity to negotiate MCC submissions (Dr Irene Opfou, MCC, 90% of submissions have some deficiency)
- Approvals (6-18 months)
- Amendments (3 months)
- Ethics committees: strong in certain universities, ?
Proactive eg microbicides

Future Directions



Disease Progression in Sero-Convertors in Africa

	Cote d'Ivoire (Salaman R, JAIDS, 2002)	Southern Africa (Gray CM, AIDS Research and Human Retroviruses, 2005)	Ethiopia (Rinke de Wit, TF, JAIDS, 2002)
	N=104 Male=83	N=51 Male=9	N=20 Men=11
	Sub-type CRF02-A/G	Sub-type C	Sub-type C
Median viral (RNA copies/ml)	4.6 log₁₀	4.08 log₁₀	4.07 log₁₀ (3 months)
time after sero-conversion		2-24 months	204 days
Median CD4	527	376	433 (3 months after sero-conversion)

HVTN 503

Update on enrolment:

- 602 enrolled
- 272 (45%) women
- 168 (28%) 18-20 years
- 366 (61%) 21-30 years
- Co-enrolment
- Pregnancy
- Undiagnosed illnesses



We're looking for some everyday heroes to volunteer for an HIV vaccine study. You can't get HIV or AIDS from this vaccine. So, if you want to see AIDS stopped in its tracks, don't wait another minute to say, "tell me more!"

More than 5,5 million South Africans are infected with HIV/AIDS. A vaccine against HIV offers the best hope in ending this global epidemic. Phambili is the first chance to be involved in a research study to examine whether an HIV vaccine works.

Since we don't know if the vaccine will protect you, everyone is asked to practice safe sex whilst participating in the trial. A total of 3 000 people will participate in Phambili in five sites around South Africa: Cape Town, Durban, Klerksdorp, Medunsa and Soweto.



Developing an HIV Vaccine:

Our goal is to find a preventative vaccine that will protect all people against HIV, the virus that causes AIDS.



The HIV vaccine currently being tested in humans is made in a laboratory and CANNOT cause HIV infection.

Vaccines usually work in one of two ways. They either prevent infection or they prepare the immune system to fight an infection after it enters your body. This vaccine is more likely to work in the second way. This could mean that the vaccine would result in a person taking longer to get sick with AIDS.

The long-term goal is to develop a vaccine that is 100% effective and protects everyone from infection. Even when a successful HIV vaccine is developed, it will still be important to educate people and get them to practise responsible sexual behaviour.

This vaccine has already been studied in more than 2000 people in Africa, North America, South America and Australia. The results of this study will guide future research, hopefully bringing us closer to a vaccine against HIV. Independent reviewers will monitor the safety of the volunteers.

You cannot get HIV or AIDS from the vaccine being studied.

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AIDS will be **stopped** by **South Africans** **like you!**



PHAMBILI

Looking forward to a better future

www.phambili.org.za

Acknowledgments

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 - Devan Mehrotra
 - Michelle Miller
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- SAAVI
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