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COMPETING INTEREST OF FINANCIAL VALUE \geq £1,000:	
Speaker Name	Statement
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The science of transmission of HIV via breastmilk

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BHIVA, London, November 2013

PMTCT research, 1994-2012

1994

2012

1994 U.S. AZT Trial ACTG 076

1998 Thai Bangkok short AZT

1998 Cote d'Ivoire short AP/IP AZT trials (Bfeeding)

1999 PETRA trial AZT+3TC

1999 HIVNET 012/Uganda single dose NVP (moms&nn)

2000 Thailand PHPT-1 Long vs short AZT

2003 ANRS DITRAME + AZT/3TC /NVP

2004 Thai trial PHPT-2 AZT & NVP

2008 PEPI NVP + short vs long AZT for bfeed infant

2008 SWEN NVP PreP for bfeed infant

2009 Mma Bana: ART vs Prep CD4<200

2010 BAN: ART vs PreP (CD4>250)

2011 Kesho Bora: ART (CD4>350, Bfeeding)

What has been acquired from PMTCT research

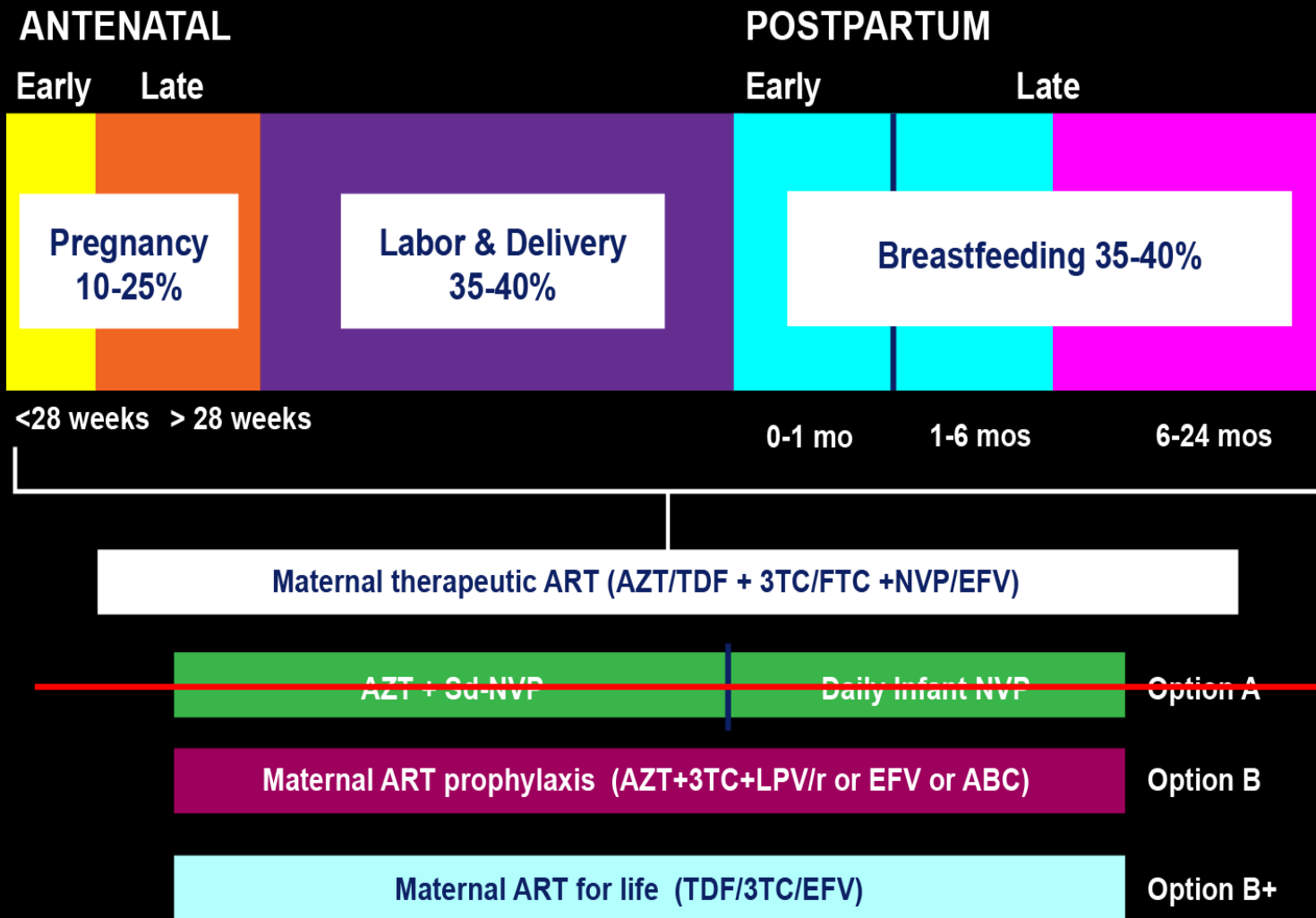
- **Prevention of de perinatal HIV transmission:**

- ✓ Early initiation of prophylaxis during pregnancy;
- ✓ Combination ARTs are more effective than monoprophyllactic regimens;
- ✓ Some drugs are more efficacious, some may be hazardous (Efavirenz and neurological defects)* ;
- ✓ The target of elimination (MTCT < 5%) seems achievable, if no breastfeeding.

- **Prevention of postnatal (breastfeeding) HIV transmission:**

- ✓ No prophylactic trial covering the whole duration of breastfeeding exposure (= 12 months);
- ✓ Important residual transmission (3,6% at 6 months in the Kesho Bora trial);
- ✓ Concerns about adherence ;
- ✓ The target of elimination seems out of reach.

WHO guidelines for PMTCT and infant feeding (June 2013)



... but research on breastfeeding transmission should continue!

June 2013 UN guidelines? A critical analysis

- Alarming inflation in the number of WHO-UNICEF PMTCT recommendations ('90s: n=1, 2000s: n=4, 2011-2013: n=2);
- Current WHO PMTCT recommendations are not evidence-based;
- Push for option B+ is based on mathematical models, best guess estimates on feasibility but NOT on measured efficacy or efficiency.

Option B or B+ ?

- **Suboptimal efficacy on postnatal transmission** in the Kesho Bora trial: in mothers with $> 350 \text{ CD4}/\mu\text{l}$, 6-month efficacy = 29% (NS)*;

Exception of the « TasP dogma »?

- **Suboptimal adherence**: in a metanalysis of more than 20,000 pregnant women, adherence of 53% at 12 months post partum**;
- **Extremely high rate of resistance in infants who get HIV-infected despite maternal prophylaxis*****

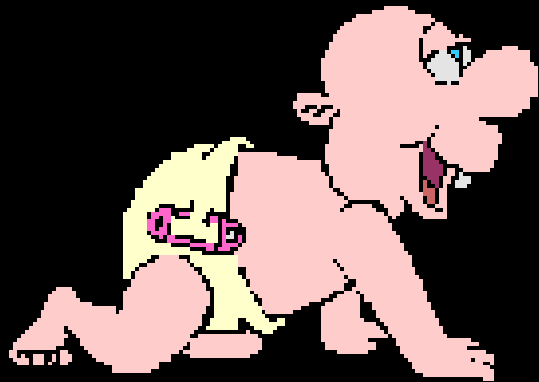
* Kesho Bora Study Group, Lancet Infect Dis, 2011

** Nachega et al, AIDS 2012

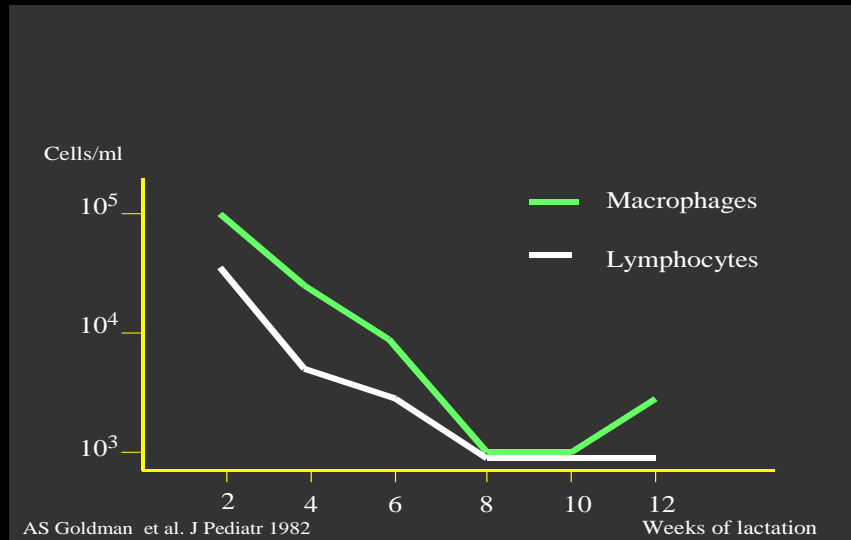
*** Zeh, PlosMed 2011; Fogel, Clin Infect Dis 2011; Lidström, CROI 2010

Mechanism(s) of breastfeeding transmission of HIV: the moving target

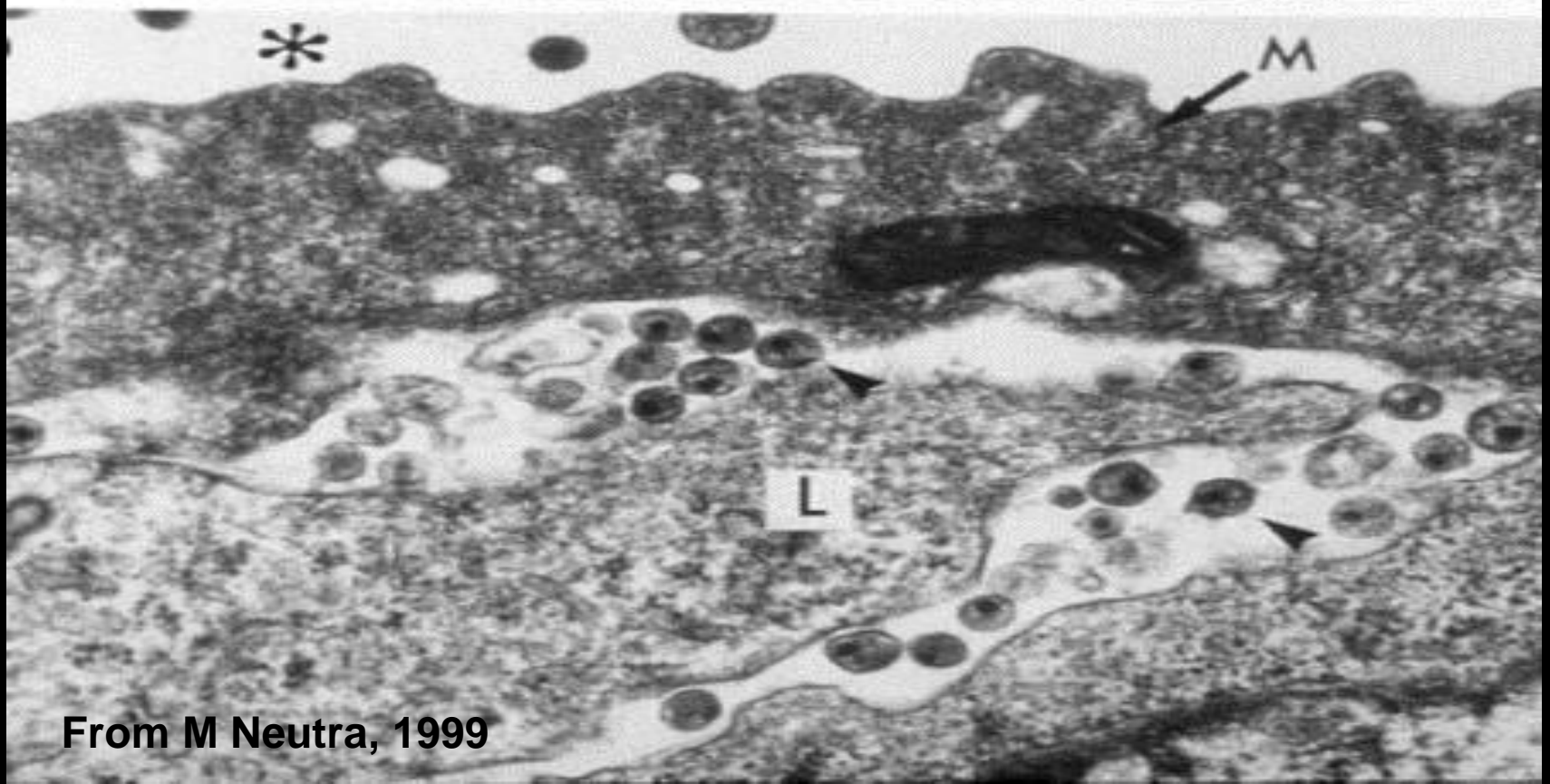
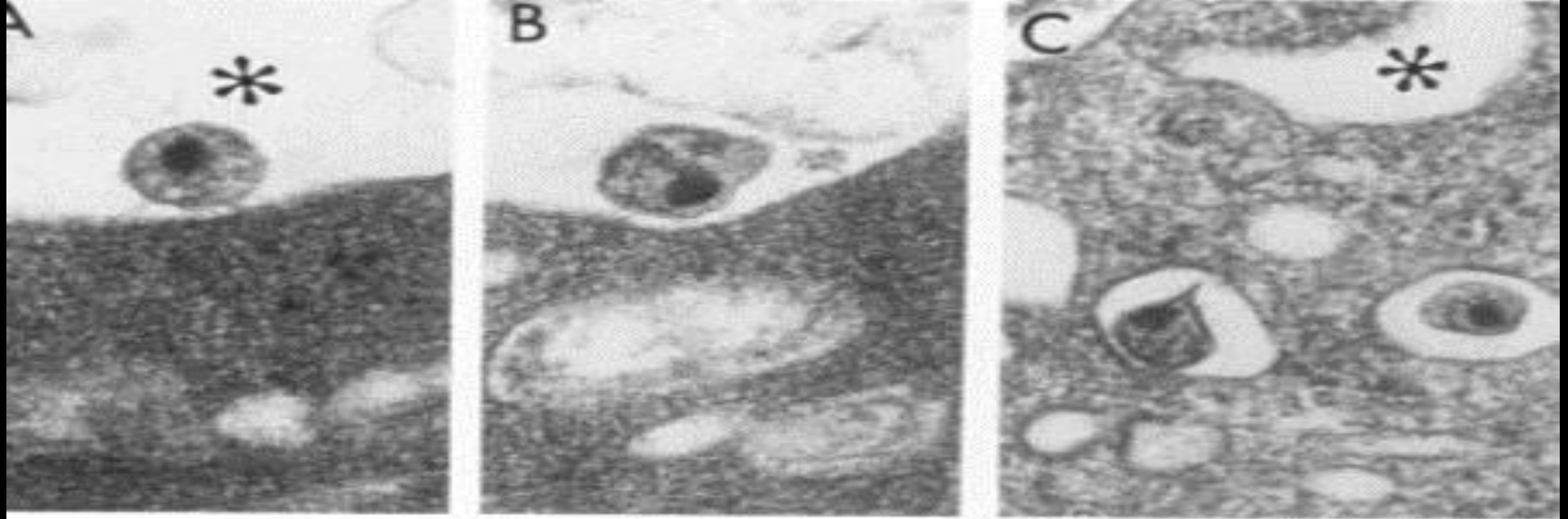
An evolving host



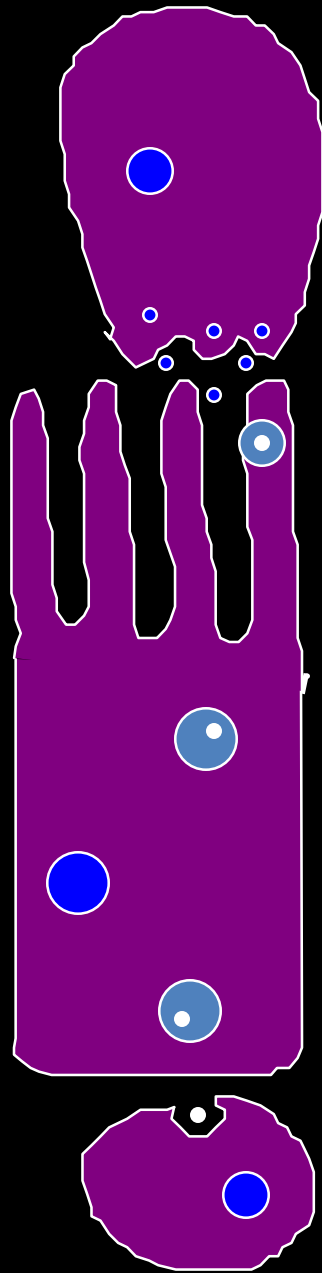
A complex and biologically active source of infection



Portal of entry

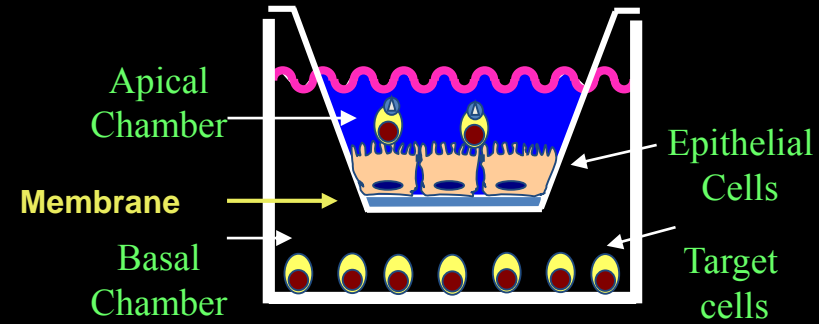


From M Neutra, 1999



Polarised HIV-1 infected cell

Gal Cer



Transcytosis in an enterocyte

Macrophages, lymphocytes and dendritic cells in the *lamina propria*

M Bomsel, 1997

Transcytosis of HIV-1 across human enterocytes

- Concept of **viral synapse**
- HIV-1 gp41 recognises a membrane **agrin** (heparan sulfate proteoglycan) that favour interaction with **GalCer** and mediate transcytosis through an **integrin** associated mechanism



Breastfeeding transmission
of HIV-1: by free virions
or by HIV-infected cells?

Cumulative HIV-1 RNA exposure in HIV-1 infected and non infected infants between 6 weeks and estimated age of HIV acquisition

ANRS 1271 Study / VTS

Cumulative HIV-1 RNA exposure until HIV infection	Case	Control	p-value
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Total; N=36 pairs

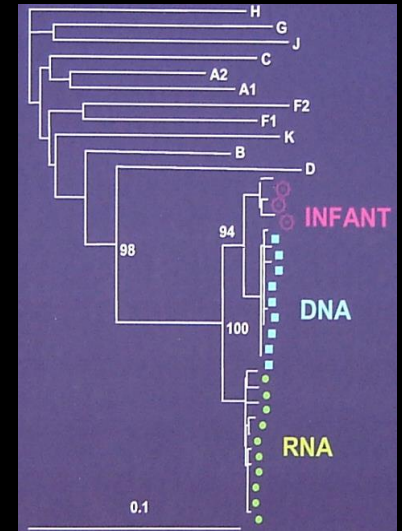
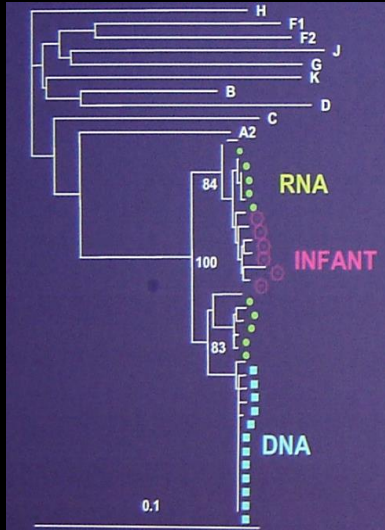
	19.65 * 10⁷	1.30 * 10⁷	<0.001
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Maternal antenatal CD4 >350 cells/ μ l; N=14 pairs

	14.86 * 10⁷	1.27 * 10⁷	<0.001
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Cell-free and cell-associated HIV-1 are both responsible for breast milk transmission

(I Koulinska, 2006)



HIV-1 Transmission

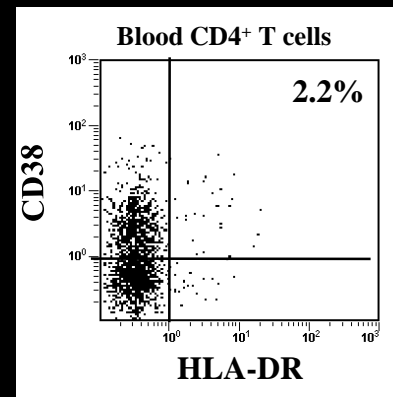
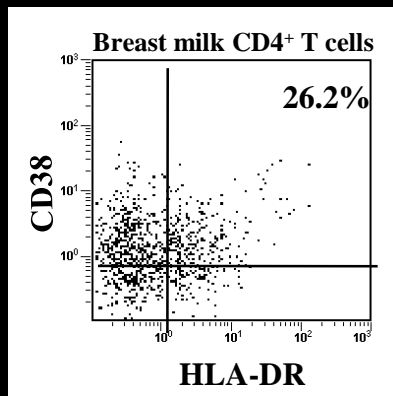
	Cell-free virus	Cell-associated virus	indetermined
< 9 m post p	2	8	6
> 9 m post p	11	8	5
Total	13	16	11

p=0.03

Characteristics of T and B lymphocytes from breast milk

Compared to blood, breast milk T and B lymphocytes are

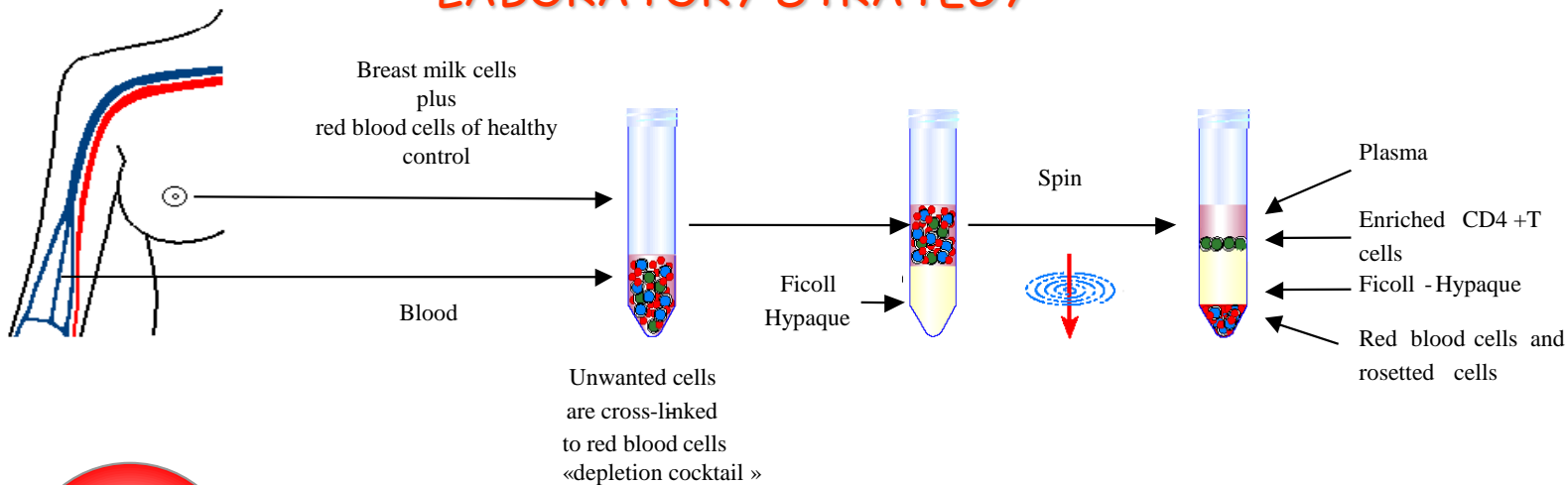
- More frequently memory cells (less naive cells)
- More often activated
- Express markers of homing signaling their mucosal origin



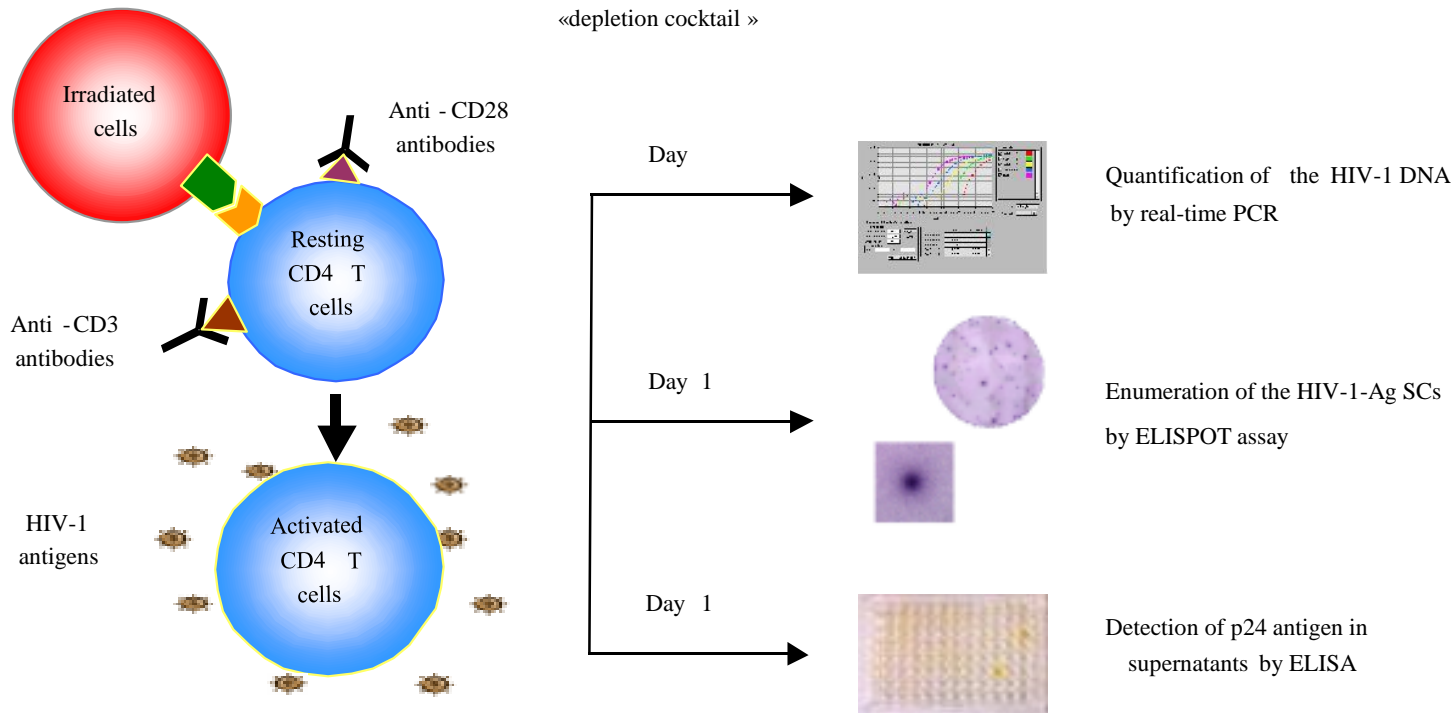
(E. Tuaille et al; J Immunol 2011)

LABORATORY STRATEGY


A



B



Proportion of latently infected cells able to enter viral cycle

	Blood	Breast milk
HIV-1 DNA copies per 10^6 T CD4+ cells	6.948 (2.351-23.043)	4.788 (2.590-47.294)
HIV-1 Ag secreting cells per 10^6 T CD4+ cells	45 (9-108)*	500 (205-934)*
		
% of HIV-1 infected T CD4+ cells entering viral cycle	0,9 - 1,8%	10,4 - 32,4%

Cell activation in breast milk:

- Associated with reactivation of CMV and EBV
- Consistent with cytokine and proteome profiles

Productively infected CD4⁺ T cells from BM

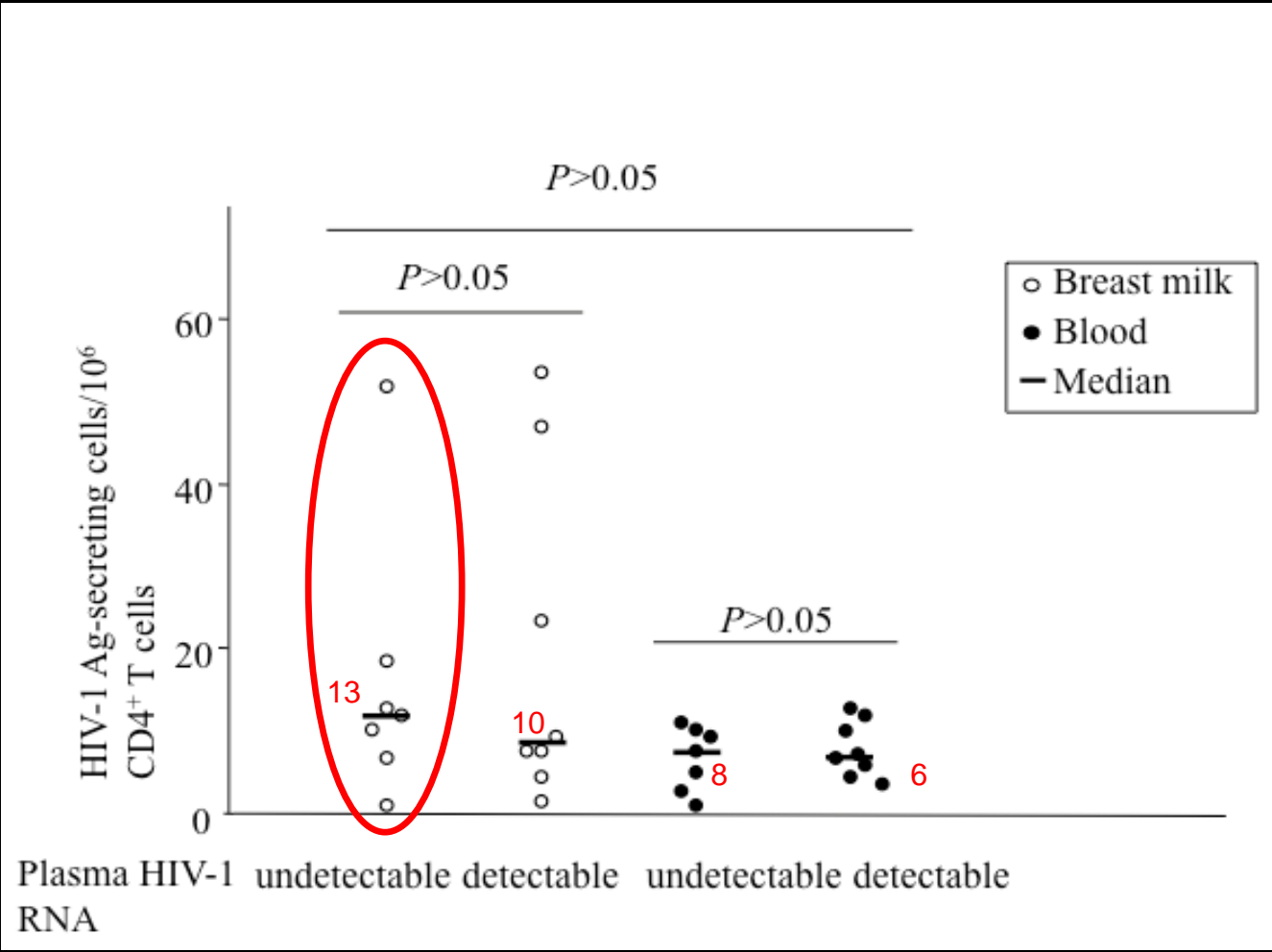
	Breast milk	Blood
HIV-1 DNA copies/10 ⁶ CD4 ⁺ T cells	2886	2240
HIV-1-Ag-SC/10 ⁶ CD4 ⁺ T cells (with undetectable HIV-1 RNA)	13	8
HIV-1-Ag-SC/10 ⁶ CD4 ⁺ T cells (with detectable HIV-1 RNA)	10	6

Viral antigens, RNA copies and infectious virus are detected in cell culture supernatants

Valea D et al, Retrovirology 2011

Cells are either activated within BM and the mammary gland or during migration from mucosal inductor sites

Productively infected CD4⁺ T cells are detectable in ART-treated women with undetectable HIV-1 RNA in blood and breast milk



Antiretroviral drugs in breast milk

Antiretroviral drugs in breast milk of HIV-1 infected women

% Breast milk / plasma

0 %

100 %

200 %

400 %

ZDV (117-140%)

d4T (173%)

3TC (300-420%)

RTV (11%)

LPV (11-21%)

NFV (21%)

NVP (67-82%)

NRTI

PI

NNRTI

* = detectable levels in baby's blood
but at very low concentration

Rezk NL, Ther Drug Monit 2008
Schneider S, JAIDS 2008
Miroshnick M, AACT 2009
Shapiro RL, JID 2006

Infant PreP (Option A) ?

- **Until now, unknown efficacy** if infant PreP is extended during the whole duration of exposure (12 months breastfeeding recommended by WHO);
- **Adherence and tolerance** uncompletely explored;
- Results of the **ANRS 12274-PROMISE-PEP** trial

BAN trial (Malawi)

- HIV-infected pregnant women, CD4>250/ μ l, breastfeeding for max 28 weeks, N=2.369
- Comparison
 - mothers: AZT/3TC/[NVP or NFV or LPV/r]
 - infant: PreP NVP (max 28 weeks)
 - control: perinatal prophylaxis only

<u>At 28 w:</u>	Postnatal transmission (2 to 28 w)	Inf HIV+ or death	
ART in moms	2.9% (1,9-4,4) (n=21)	4.1% (2,9-5,8)	P=0,07
PreP in infants	1.7% (1,0-2,9) (n=12)	2.6% (1,7-4,1)	
Control	5.7% (4,1-8,0) (n=32)	7.0% (5,1-9,4)	

ANRS 12174 trial – preliminary data

- Randomised trial of infant PreP extended up to 12 months, 3TC versus LPV/r; Burkina Faso/Uganda/Afrique du Sud/Zambie
- N=1273; Follow up will be completed in April 2013;
- July 2012: unblinded analyses on transmission, tolerance and mortality on the 788 infants aged 12 months or more;
- **D7-M12 HIV-1 Transmission rate: 1,1% (95% CI: 0.6-2.2), including 6/9 infections after 6 months (D7-M6 transmission: 0.3%)**
- **Overall MTCT rate: 1.8%, well within the target of elimination !**
- **12 months mortality: 3.2 per 100 inf-yr (95% CI: 1.8-4.5)**
- ✓ **12 months HIV-free survival : 96% (95%CI: 94-97)**
- ✓ **SAE: 188, none attributable to PreP**

Conclusions:

- **Transmission rate is the lowest ever observed;**
- **Compared efficacy and tolerance of the 2 PreP regimens will be known in December 2013**

Conclusions (1)

1. Do not throw Infant PreP (option A) with the baby's bath
2. Evidence based versus best guess or model-based international recommendations?
3. Future research ?
 - How to operationalise the access to prevention and therapy within national programs?;
 - How to optimise existing PMTCT regimens?;
 - Infant PreP: a place for long acting ARV drugs?

What about tomorrow?

STR-based ART in all HIV infected pregnant women eligible

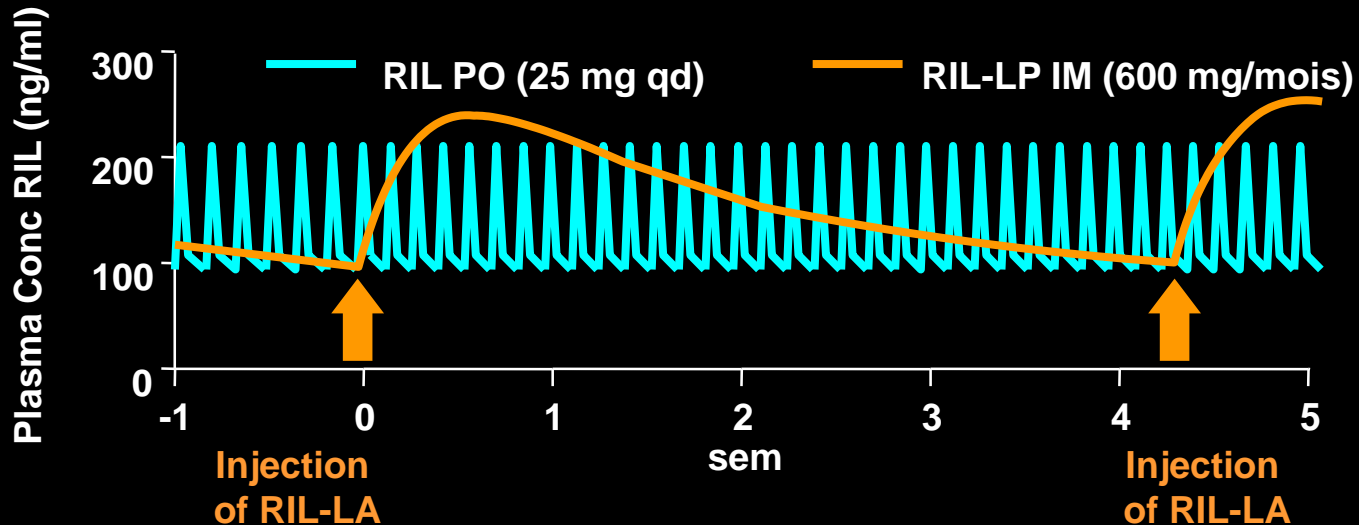


Infant PreP with a long acting drug covering the whole duration of breastfeeding

Examples: Rilpivirine LA*, GSK744**

* Van 't Klooster G, AAC 2010

** Andrews C et al, CROI 2013, Atlanta



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