How to prevent Mother to Child Transmission of HIV ….

Montpellier 2008

EACS HIV course

Dr Roland TUBIANA
Service Maladies Infectieuses
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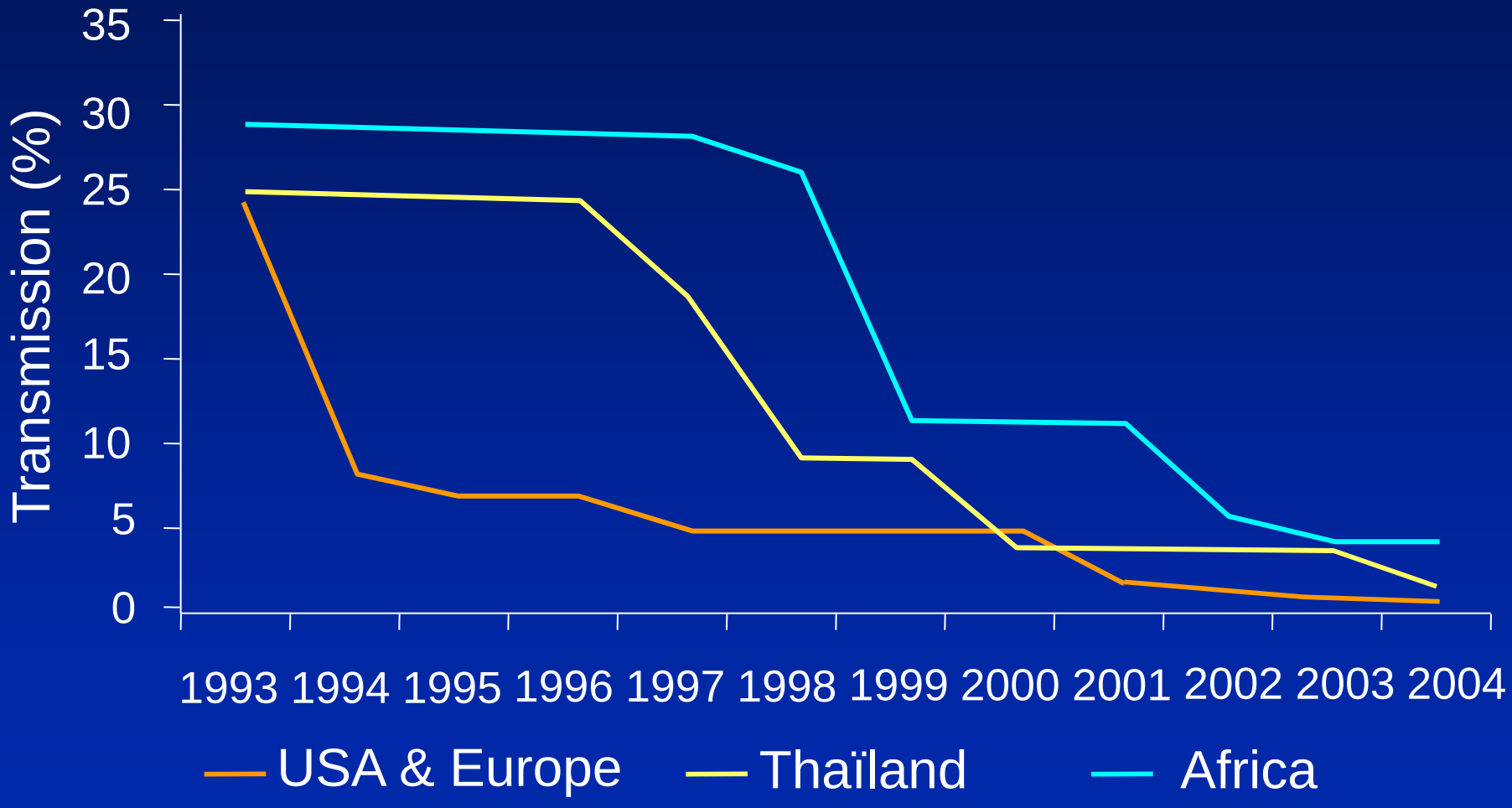
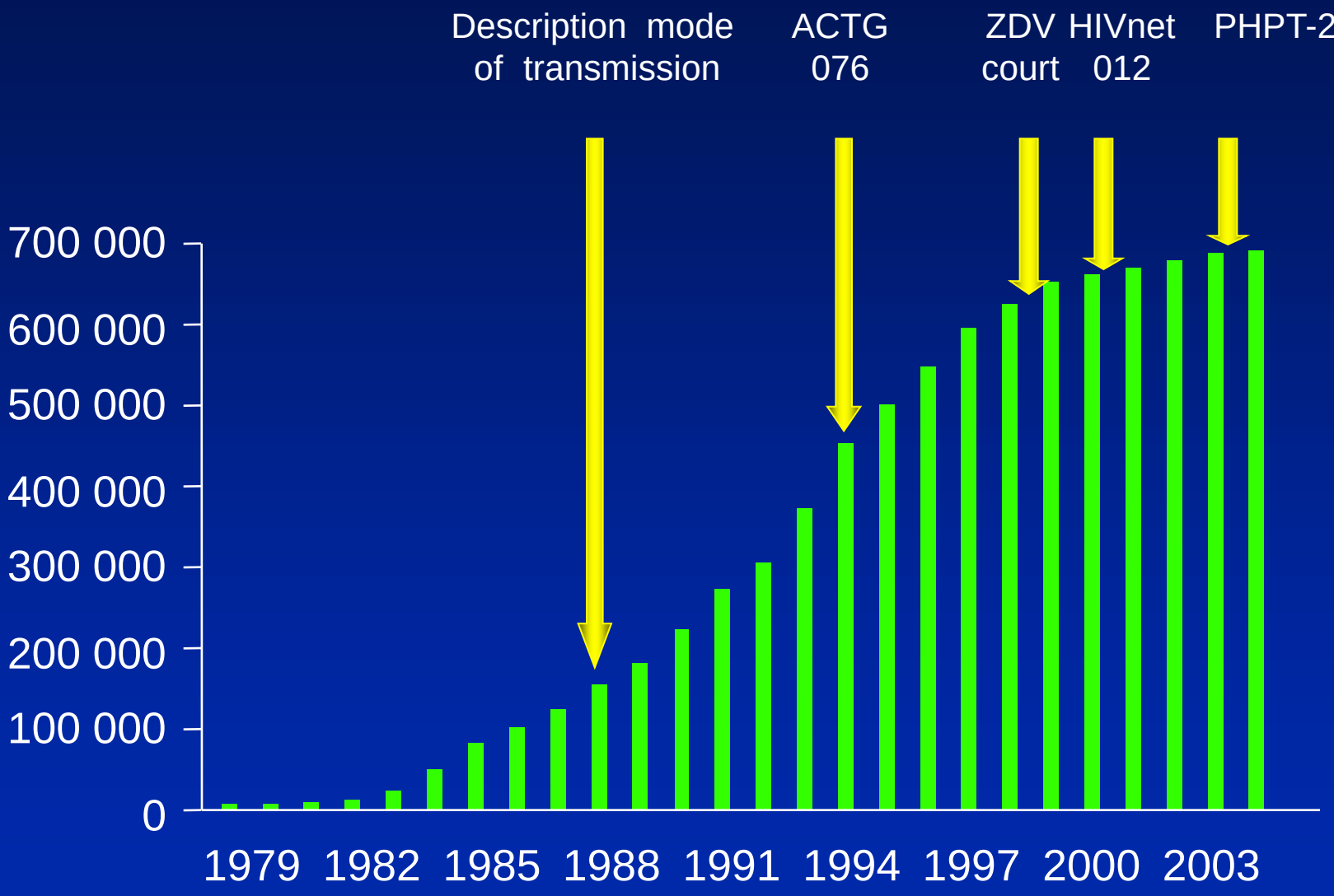
HIV-MTCT rate in clinical trials



McIntyre J., CROI 2005, Abs. 8

Estimation of newly infected children/year

2000 children /day in 2005 (mostly MTCT)



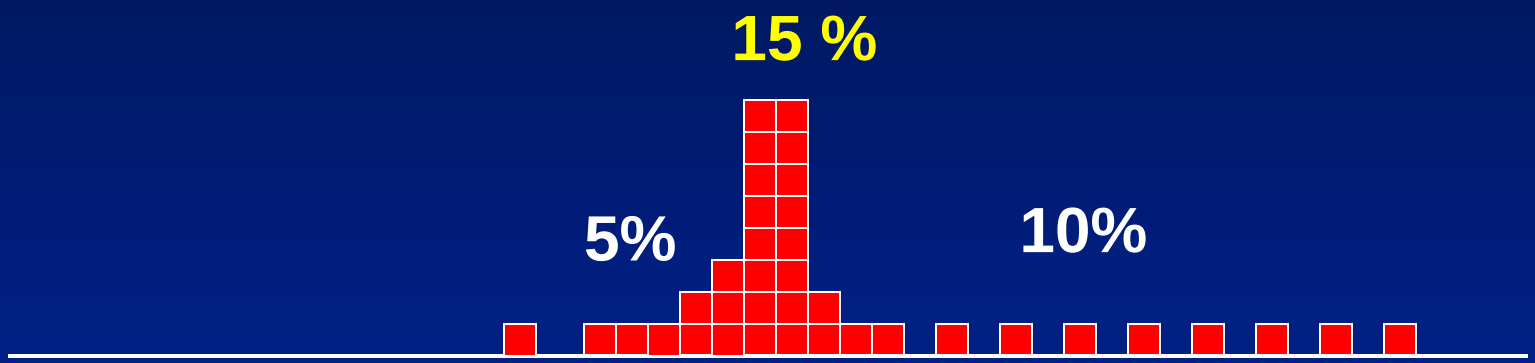
McIntyre J., CROI 2005, Abs. 8

"We have the tools and we have to more forward…" **Elaine Abrams Toronto 2006**

- **We have failed to reach more than 90% of pregnant women needing PMTCT, predominantly those living in resource-limited settings.**

- **to increasing coverage, we need to improve the follow-up of (HIV-positive) pregnant women and their babies and to obtain outcome data for the evaluation of programs in "real-life" settings**

Timing of Vertical Transmission for 30%



Pregnancy
Pre-natal

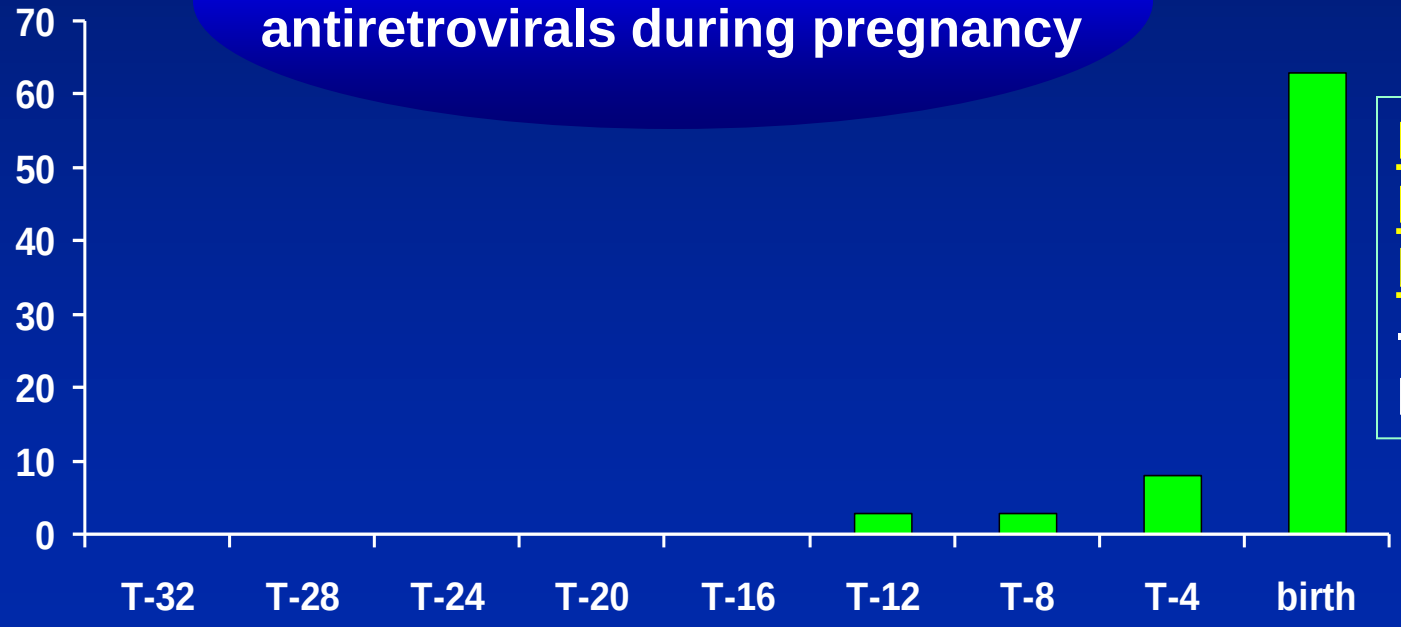
DE LIV ER Y

Breast-feeding
Post-natal

Methods to prevent HIV transmission

exposure at delivery
antiretrovirals
elective C-section

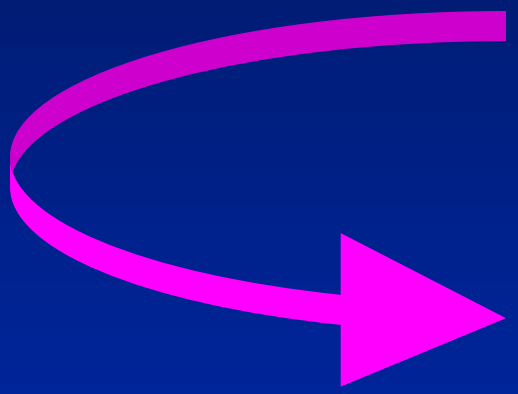
plasma viral load
antiretrovirals during pregnancy



Timing of mother-infant transmission

Post exposure Prophylaxis: baby
- ART and Formula feeding

Vertical transmission of HIV



15-35%

<1%

Antenatal screen
Maternal ART
Neonatal ART
C. section
No breastfeeding

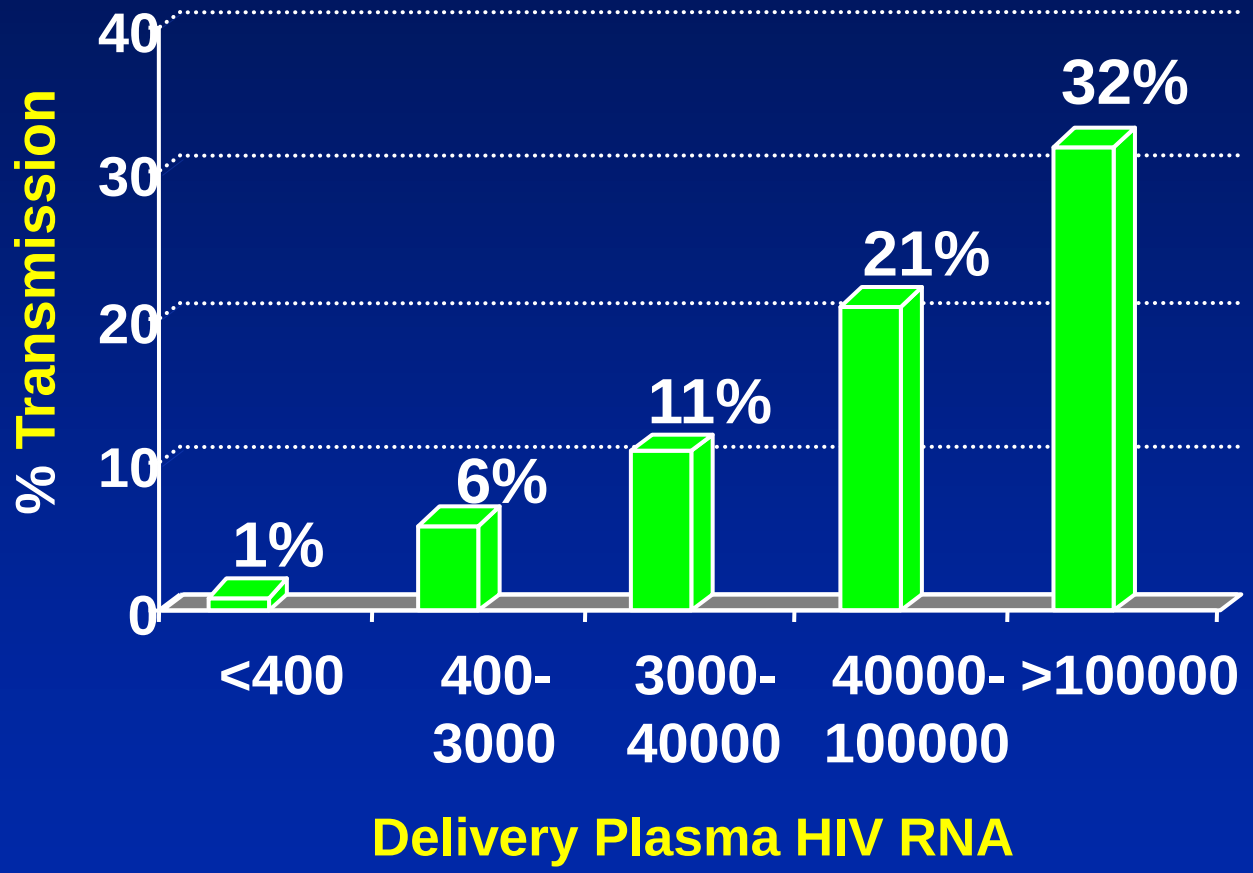
Factors Influencing Perinatal Transmission

- **Maternal Factors**
  - HIV-1 RNA levels
  - Low CD4 lymphocyte count
  - Other infections (eg, hepatitis C, CMV, bacterial vaginosis)
  - Lack of ARV during pregnancy

- **Obstetrical Factors**
- Length of ruptured membranes ~2% increased risk per hour (*AIDS, 2001)*
- chorioamnionitis
  - Vaginal delivery
  - Invasive procedures

- **Infant Factors**
  - Prematurity
  - Gender (f>m)
  - Breastfeeding ++

Pronostic value of the HIV-1 plasma viral load in absence of ART



Blattner W. XIII AIDS Conf, July 2000, Durban S Africa (LBOr4)
WITS study, 1990-1999

EPF 97-2003
4480 women (treated) : (TR = 1.3 %)
AIDS 2008,22: 289-299

HIV RNA Delivery cp/ml		Univariate Analysis			Multivariate Analysis	
	N	%transm	OR	P	OR	P
≥ 50 000	95	8.4	16.8	< 0.01	13.3	< 0.01
[10000-50000[	305	6.9	13.5		11.4	
[5000-10000[	208	1.9	2.7		2.6	
[1000-5000[	652	1.4	2.6		2.6	
[500-1000[	303	1.0	1.8		1.7	
< 500	2752	0.6	1		1	
< 50	1031	0.3				

4480 women (treated) : EPF 97-2003
Moment of ARV initiation

Initiation ARV		Univariate Analysis % transmission			Multivariate Analysis	
	N	%	OR	P	OR	P
Odd ratio by week			1.03	0.02		0.03
> 32SA	556	2.5	2.9	< 0.01		
[28-32[SA	1073	1.3	1.6			
[21-27[SA	794	1.4	1.6			
[4-20[SA	895	1.0	1.1			
Before pregnancy	1138	0.9	1			

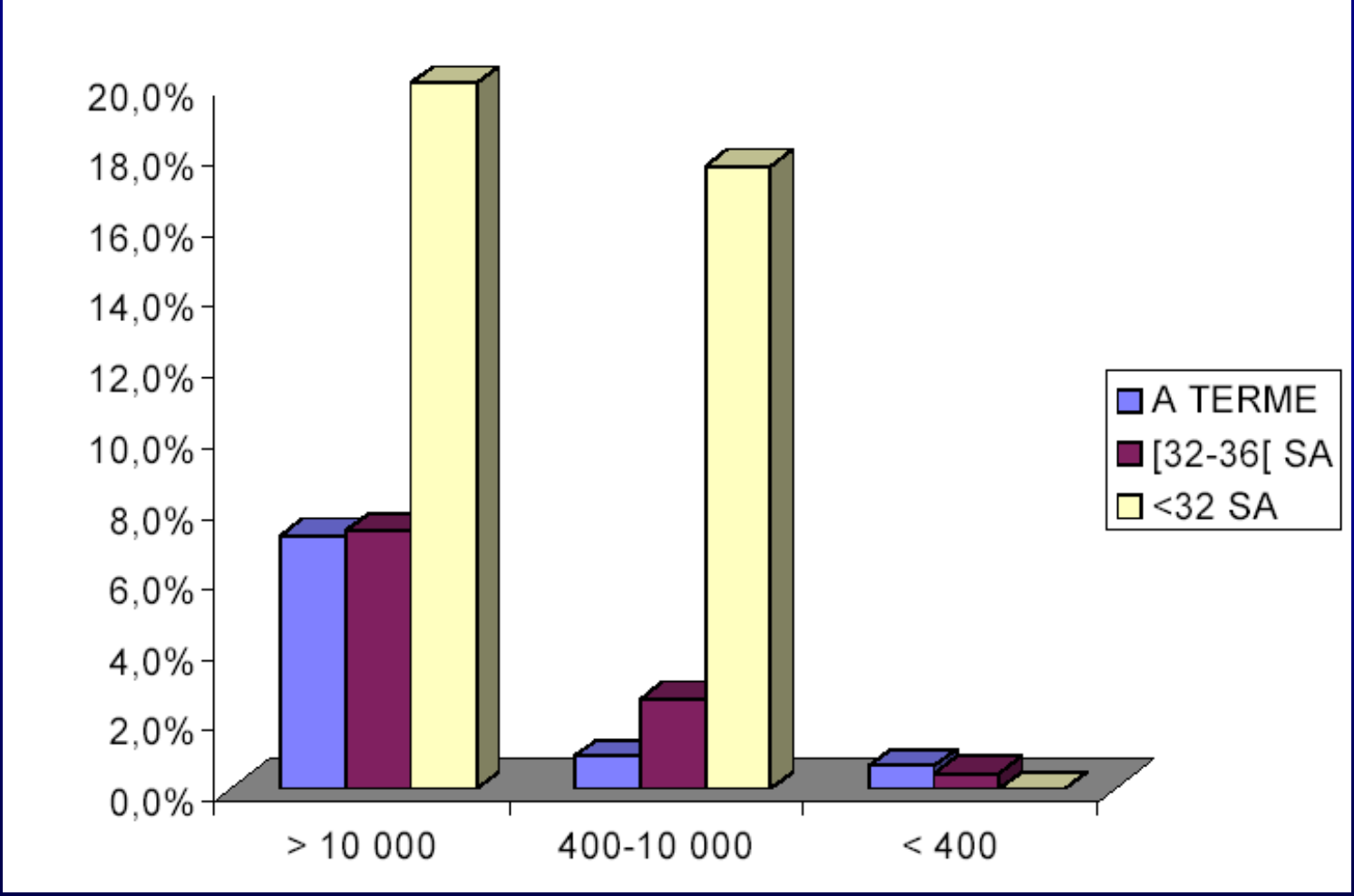
EPF 97-2003
4480 women (treated) : (TR = 1.3 %)
Prematurity and infant gender

Term Weeks		Univariate Analysis Transmission			Multivariate Analysis	
	N	%	OR	P	OR	P
< = 32	103	6.8	6.1	< 0.01	3.4	0.04
[33-37 [	463	1.3	1.1		1.1	
> 37	3914	1.2	1		1	

Sexe du Nouveau né		Univariate Analysis transmission			Multivariate Analysis	
	N	%	OR	P	OR	P
Female	2151	1.8	1.9	< 0.01	2.2	< 0.01
Male	2297	0.9	1		1	

Transmission According to prématurity And HIV- VL

EPF 1997-2003



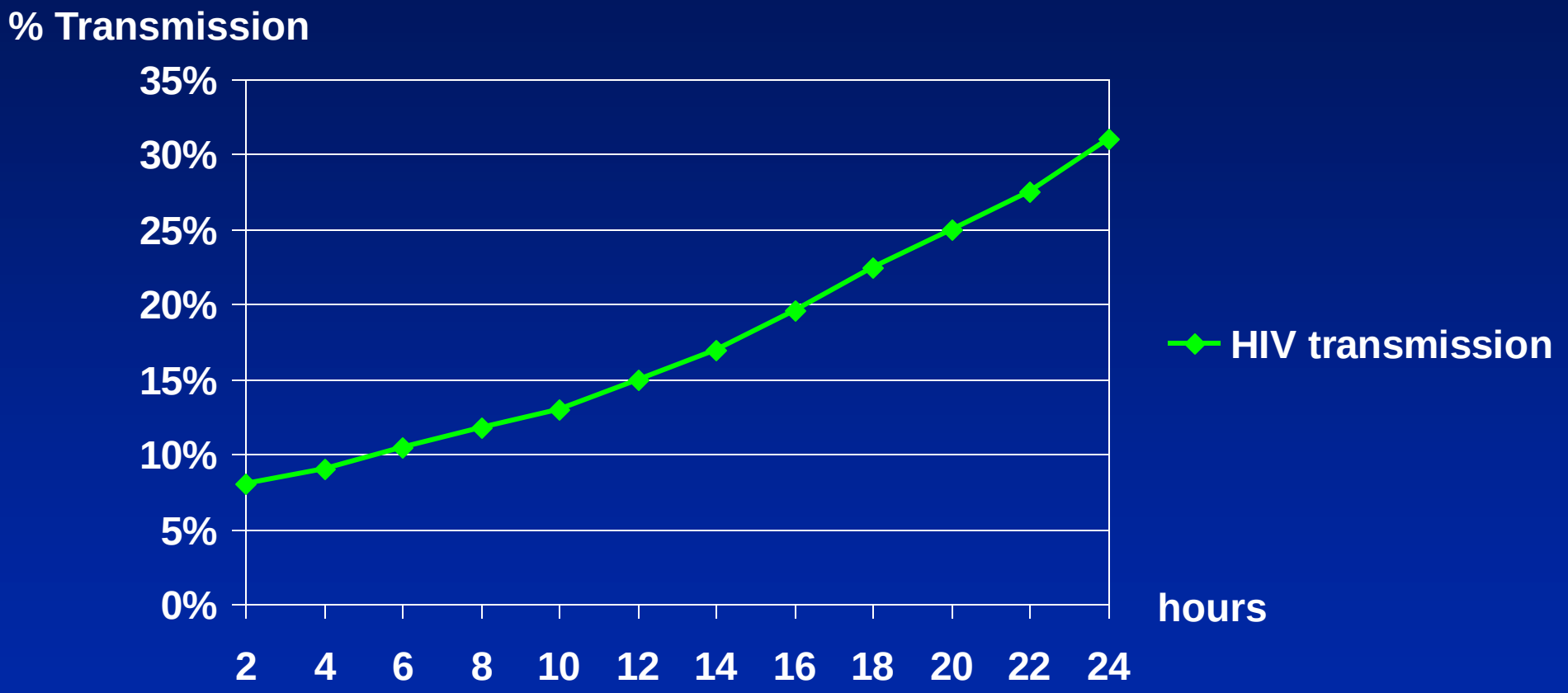
Factors affecting HIV transmission at delivery (19 cases out 560, 3.4%)

D4T+3TC +NVP from 25TH Week (if CD4>200) to 6 months post-partum (weaning)

		HIV neg	HIV pos		OR
		N	N	%	
Mother pre-HAART VL	<10,000 c/ml	283	3	1.0	6.2
	>10,000 c/ml	256	16	5.9	(1.8-21.6)
Pre-HAART Haemoglobin	> 8 gm/100 cc	465	13	2.7	2.6
	< 8 gm/100 cc	75	6	7.4	(1.1-7.1)
Place of delivery	Reference centre	318	9	2.8	1.3
	Others	242	10	4.1	(0.6-2.9)
Pre-delivery length of HAART	>80 days	214	4	1.8	2.6
	<80 days	301	15	4.7	(1.05-8.1)

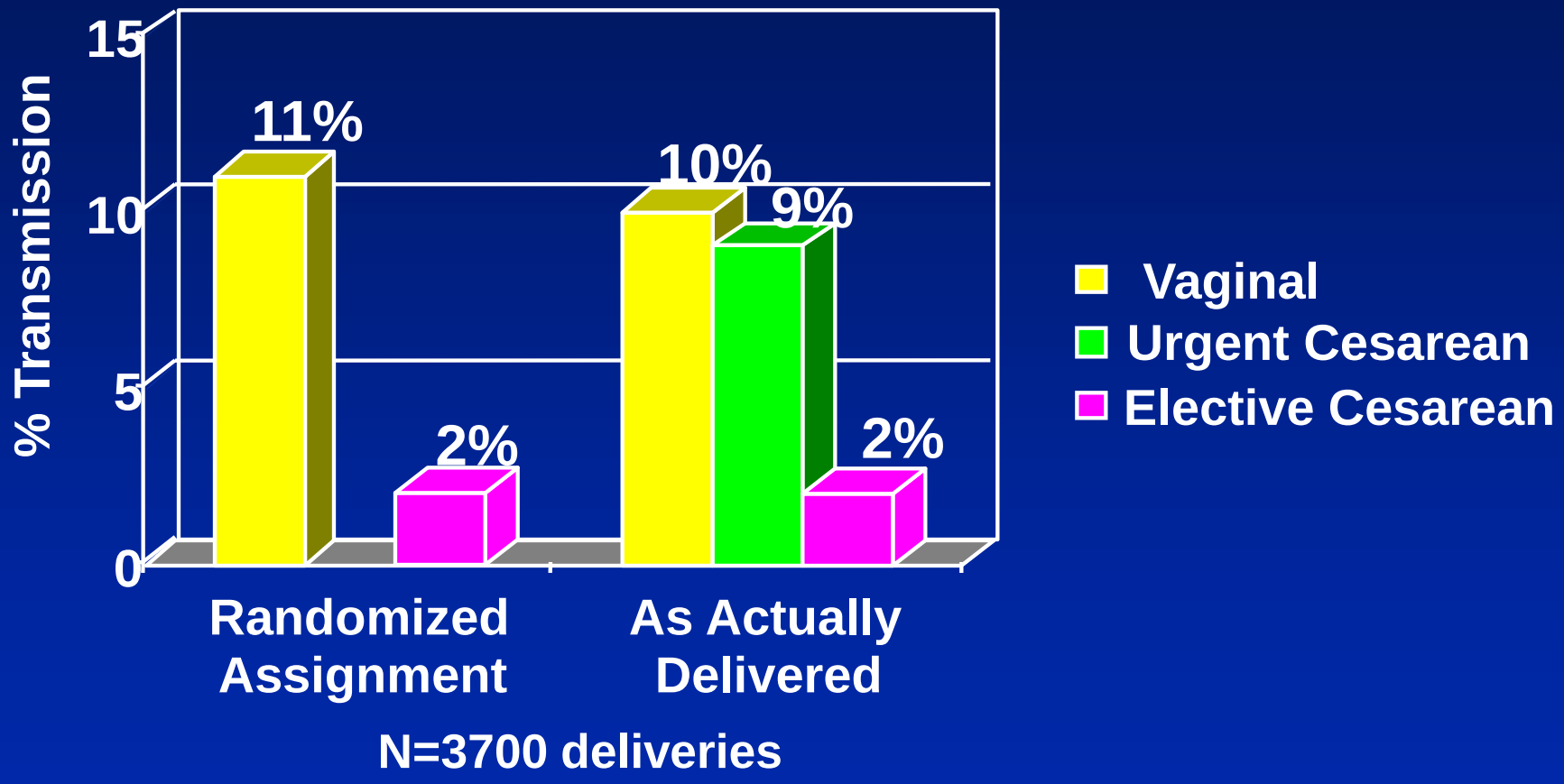
the DREAM Program
2006 Mozambique

Labor/Obstetrical Factors: Duration of Ruptured Membranes
a meta-analysis from 15 studies



*The International perinatal HIV Group. AIDS 2001;**15**:357-368*

European Randomized Mode of Delivery Trial: Elective Cesarean at 38 Weeks vs Vaginal Delivery



European Mode of Delivery Collaboration. Lancet 1999;353:1035-9

C.S. - Evidence to date: with AZT mono (ACTG 076)

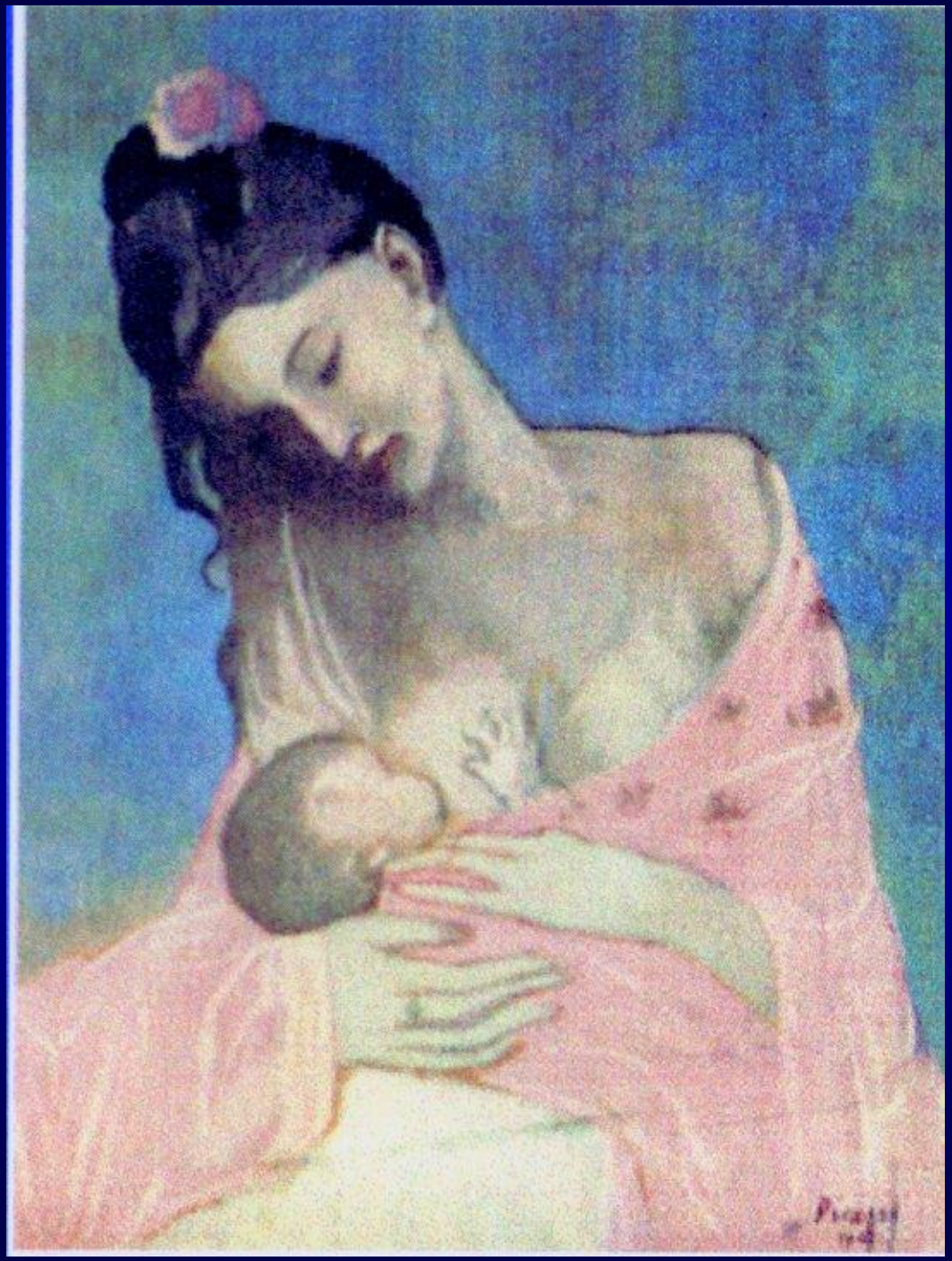
- **Metanalysis of 15 cohort studies** ***NEJM 1999***
  - **Transmission rate 8.2% Elect.C.S**
  - **Transmission rate 16.7% all other modes**
- **European Mode of Delivery Collaboration*Lancet1999***
  - **All received AZT as per ACTG 076**
  - **Transmission rate 0.8% Elect.CS**
  - **Transmission rate 4.3% vaginal delivery**
- **French perinatal cohort n=902** ***JAMA 1998***
  - **All received AZT as per ACTG 076**
  - **Transmission rate 0.8% Elect. CS**
  - **Transmission rate 6.6% vaginal delivery**

Effect of C-section on MTCT transmission n=2895 *Shapiro D, et al. #99 CROI 2004*

No difference between delivery modes in women receiving HAART

	ECS	Vaginal delivery or emergency C-section
HIV-1 RNA > 1000 copies/mL		
Single drug	1.8%	7.4% p=0.03
Multi-drug HAART	2.3%	1.8% NS
HIV-1 RNA < 1000 copies/mL		
Single drug	1.8%	4.3% p= 0.09
Multi-drug HAART	0.8%	0.5% NS

Shapiro D, et al. #99



Breastfeeding...

- Accounts for 44% of infections : More than 200.000 of the 500.000 new HIV infections that occur each year in children are the result of transmission through the mother's breast milk….

- Additional HIV transmission risk with breastfeeding
  - 14% ↑ risk in women with established infection
  - 29% ↑ risk in women with primary infection
  - Exclusive versus mixed feeding
  - cracked nipples, mastitis, infant GIT

- Women considering breastfeeding should know their HIV status
- Huge cultural issues +++

post-natal transmission of hiv Through breastfeeding

- 277 HIV infected pregnant women and their infants in Burkina Faso

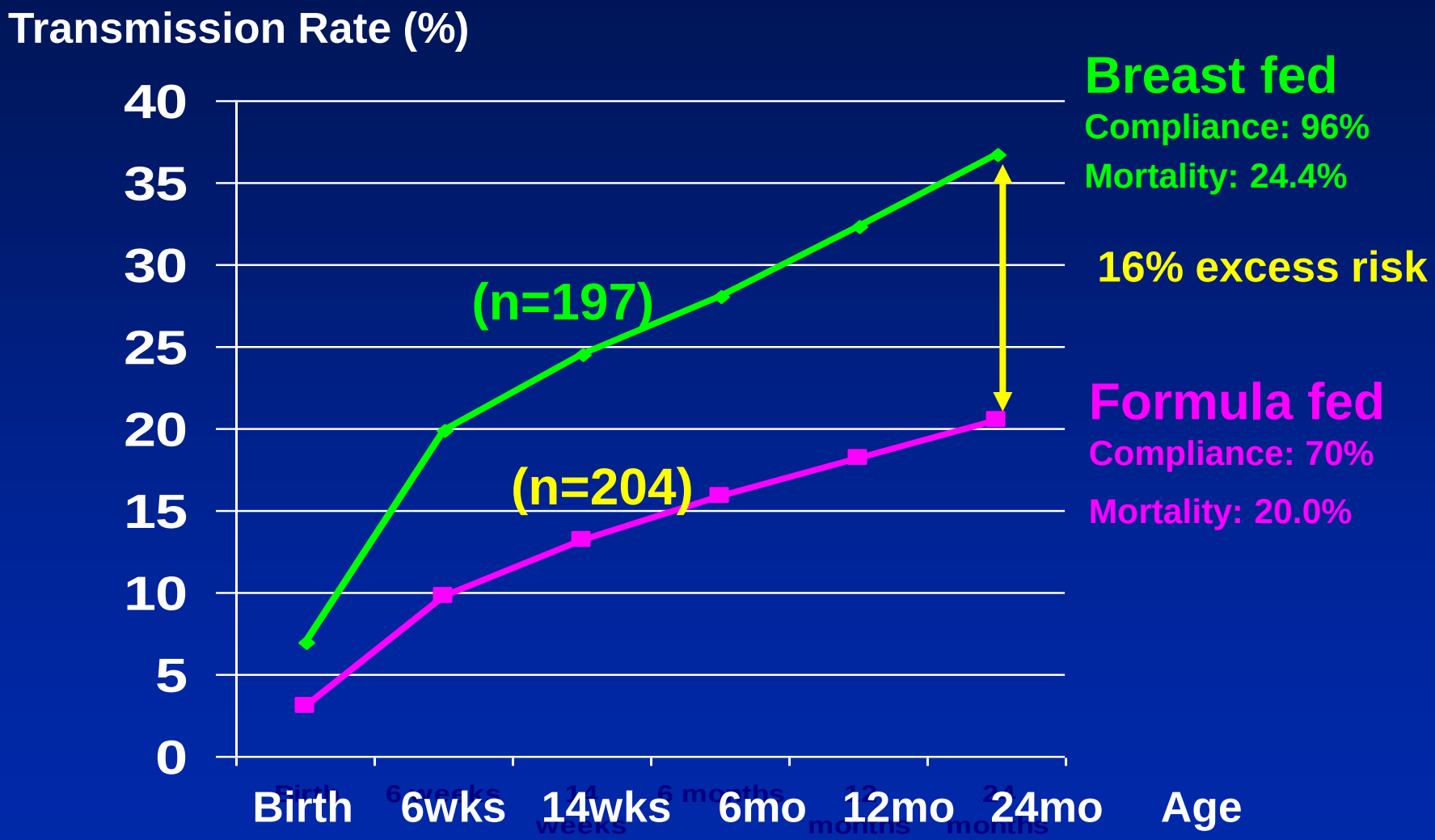
- HIV Transmission M24 24,6 %
  - *In utero* 4,0 %
  - *Per-partum* 12,1 %
  - *Post-partum* 8,5 %

- maternals risk factors
  - CD4 OR = 0,7 for + 100 CD4/mm^3
  - CV OR = 3,3 for + 1 log_{10} c/ml d'ARN VIH plasma

  Mother's milk factors
  - CV OR = 2,5 for +1 log_{10} p = 0,03

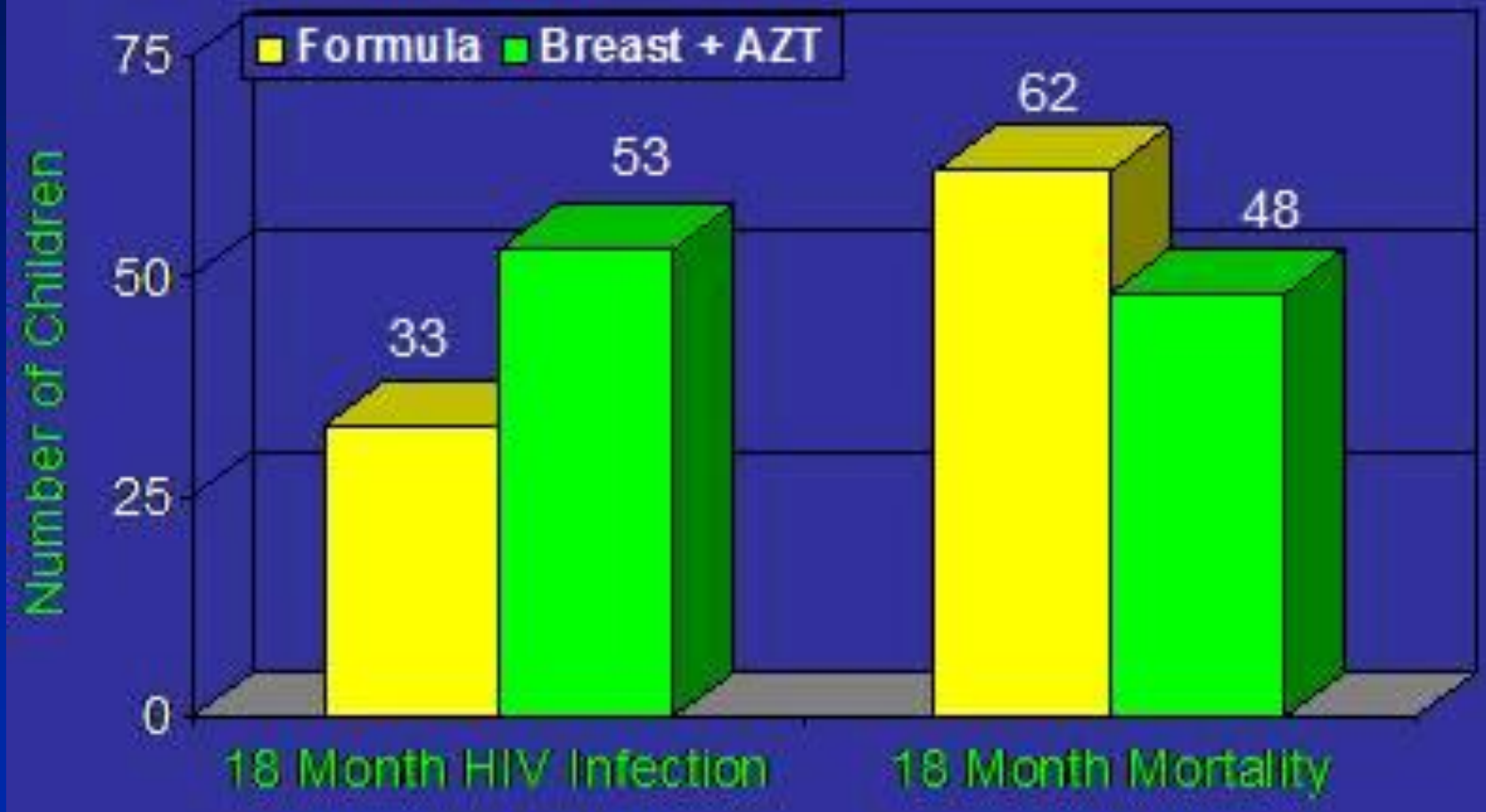
Janoff E., CROI 2006, Abs. 729

Randomized Trial of Formula vs. Breast Feeding



*Nduati R,et al. JAMA 2000;**283**:1167-1174*

AT 18 MONTHS: MORE BREASTFED INFANTS INFECTED
BUT: MORE FORMULA-FED INFANTS DIED



Thior I et al, JAMA 2006

Prevention of HIV transmission through breast feeding

- Formula feeding

- Early cessation of breast feeding

- Exclusive breast feeding ?

- Antiretrovirals in mothers/neonates

- Vaccine ??

Extended Antiretroviral Prophylaxis to Reduce Breast-Milk HIV-1 Transmission

Newton I. Kumwenda, Ph.D., Donald R. Hoover, Ph.D., Lynne M. Mofenson, M.D., Michael C. Thigpen, M.D., George Kafulafula, M.B., B.S., Qing Li, M.Sc., Linda Mipando, M.Sc., Kondwani Nkanaunena, M.Sc., Tsedal Mebrahtu, Sc.M., Marc Bulterys, M.D., Ph.D., Mary Glenn Fowler, M.D., M.P.H., and Taha E. Taha, M.D., Ph.D.

N Engl J Med 2008;359.

- At birth : HIV infection in 6.5, 7.1 and 7.1 %

FOR Mother breastfeeding and HIV neg new borns :

- Infants Randomization :

Single dose NVP plus 1 week of ZDV: 1088

Same plus daily nvp for 14 weeks : 1099

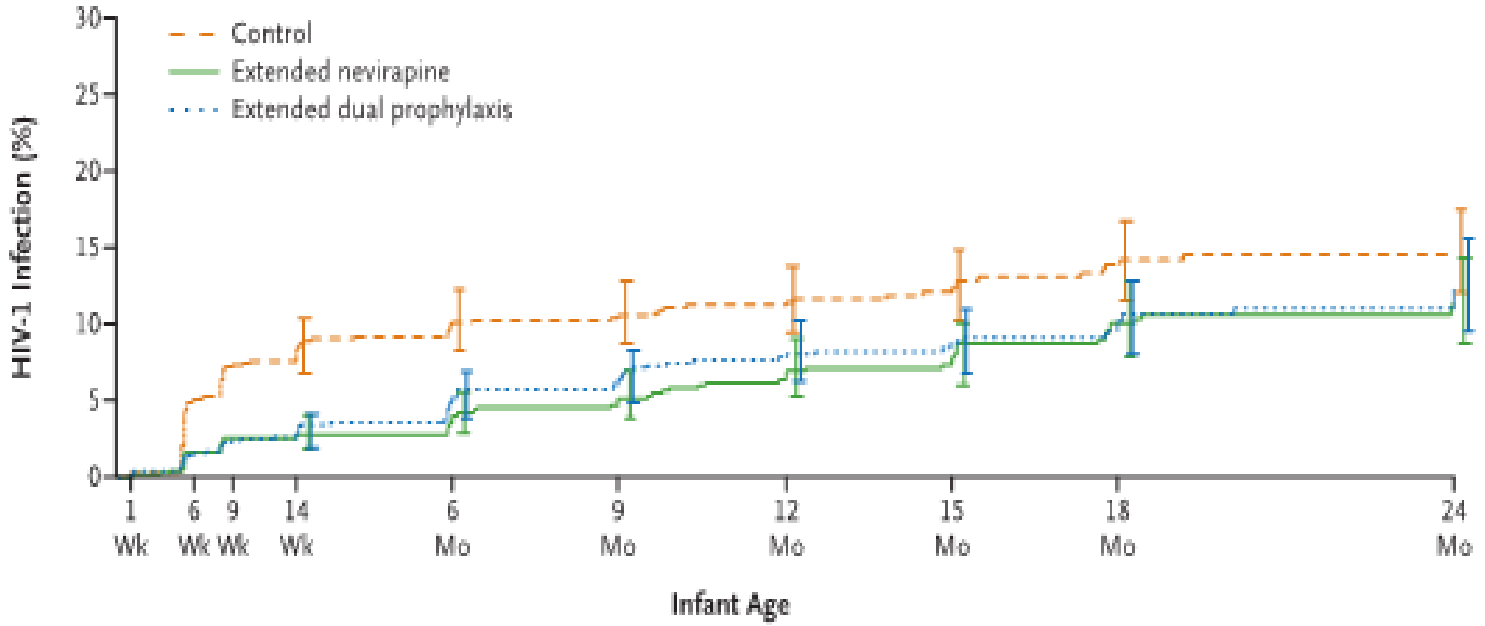
Same plus daily nvp+zdv for 14 weeks: 1089

Estimated protection of the 14W nvp group is 67% at 6 weeks, 67% at 14 weeks but 51% at 9mths

Estimated protection of The 14W nvp plus azt group is 69% at 6W , 66% at 14 weeks and 40% at 9mths

But the rates of HIV transmissions more than doubled between 9 and 24 months !!!

A

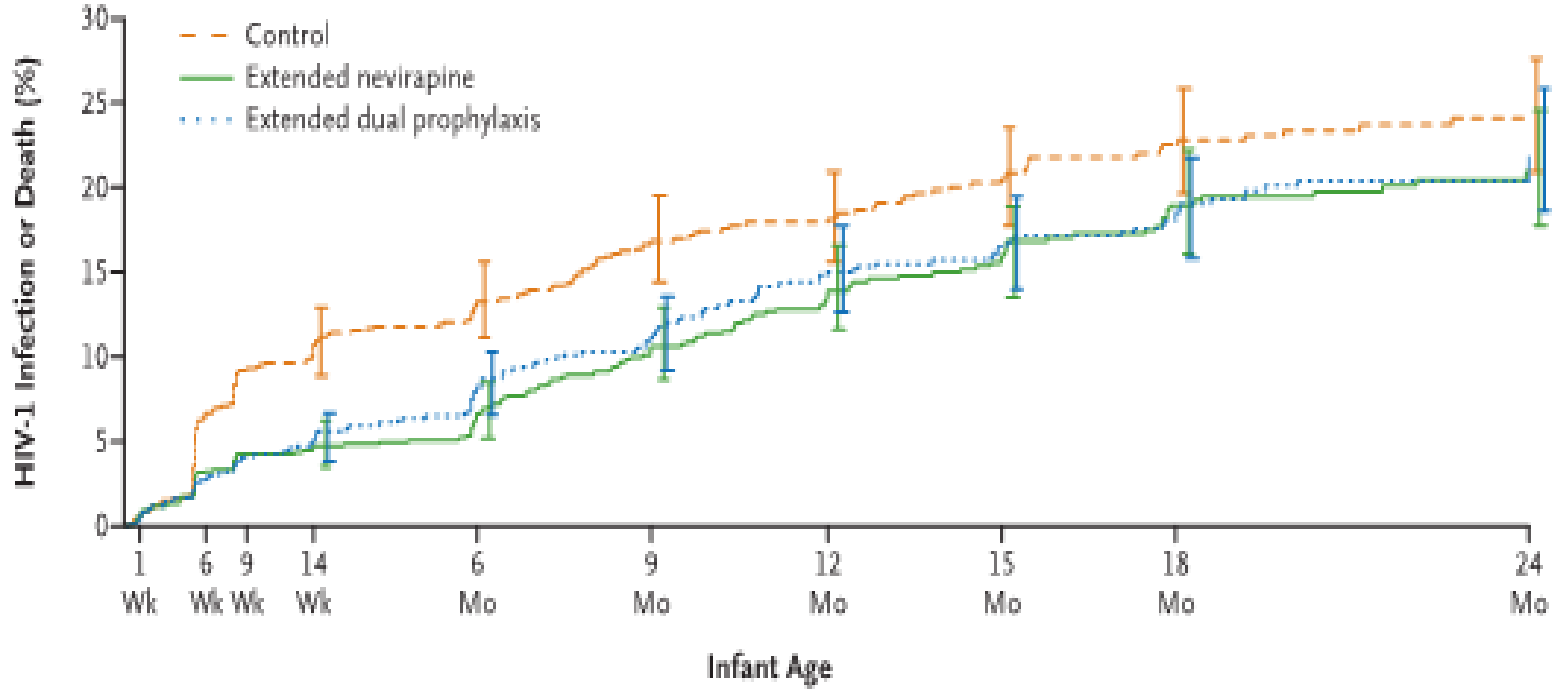


No. at Risk										
Control	992	870	813	756	660	548	454	386	302	281
Extended nevirapine	1005	934	879	812	710	593	490	412	330	161
Extended dual prophylaxis	986	904	854	803	695	589	488	416	338	145

N Engl J Med 2008;359.

HIV free survival is significantly better in both groups at 9 months but **the advantage is lost by 12 months in the NVP plus ZDV group and by 15 months in the NVP group**

C



No. at Risk										
Control	992	869	813	756	659	548	454	368	302	199
Extended nevirapine	1002	914	879	812	710	593	490	412	328	161
Extended dual prophylaxis	986	904	854	803	695	589	488	415	338	144

Table 4. Serious Adverse Events.*

Relationship to a Study Drug	Control Group (N=1003)		Extended-Nevirapine Group (N=1016)		Extended-Dual-Prophylaxis Group (N=997)		Total (N=3016)		P Value†
	No. of Infants	No. of Events	No. of Infants	No. of Events	No. of Infants	No. of Events	No. of Infants	No. of Events	
Not related	257	367	275	383	255	370	787	1120	0.69
Possibly related	37	38	44	45	62	67	143	150	0.02
Probably related	2	2	6	6	5	5	13	13	0.42
Total	278	407	310	434	299	442	887	1283	0.34‡

* The numbers of infants with at least one serious adverse event are listed. Infants could have events in more than one category.

† P values are for the overall comparison among study groups for the number of infants with serious adverse events; values were calculated with the use of Fisher's exact test.

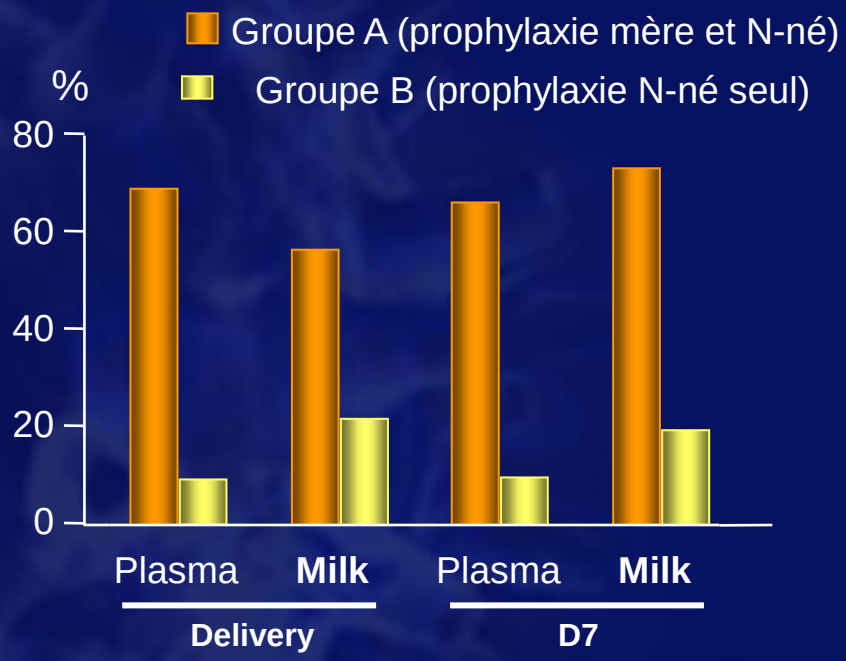
‡ P=0.14 by the Jonckheere–Terpstra test.[11]

HIV-RNA levels (median of Log) in plasma and in various milk fractions of two groups of pregnant women: group A receiving HAART; group B do not receiving any ARV drugs (Dream)

	GROUP A (n=40)	GROUP B (n=40)	
Delivery			
Log HIV RNA in plasma, median	2.2	4.8	p<0,005
Log HIV RNA in whole milk, median	2.3	3.4	p<0,005
Log HIV RNA in lipid fractions, median	1.7	3.1	p<0,005
Log HIV RNA in milk overflow, median	2.5	3.4	p<0,005
Day 7			
Log HIV RNA in plasma, median	2.3	4.9	p<0,005
Log HIV RNA in whole milk, median	1.9	3.6	p<0,005
Log RNA HIV in lipid fractions, median	1.7	3.5	p<0,005
Log HIV RNA in milk overflow, median	1.7	3.9	p<0,005

Reduction of HIV load in breastmilk after prepartum and postpartum treatment

% CV < 400 c/ml



ARV Concentrations à D0 and D7

Médiane	Plasma mg/l	Lait mg/l	Rapport lait/plasma
NVP			
J0	2,9	2,5	0,7
J7	4,0	2,1	0,6
3TC			
J0	< 0,01	0,2	1,2
J7	0,1	0,3	2,3
ZDV			
J0	< 0,02	< 0,02	0,9
J7	< 0,02	< 0,02	1,1

Giuliano M., CROI 2006, Abs. 727

ETUDE AMATA SUR LA TRANSMISSION VERTICALE POST NATALE DU VIH =
ETUDE DE COHORTE COMPARANT L'EFFICACITÉ DE LA TRITHÉRAPIE DURANT L'ALLAITEMENT AVEC LE LAIT ARTIFICIEL

- Lux-Development/Initiative ESTHER,
- Treatment and Research on AIDS Center Rwanda,
- Laboratoire Nationale de Réference, Kigali, Rwanda
- Ministère de la santé

AMATA Study:

- Amata means milk in Kyniarwanda
- may 2005 /Dec 2007
- Children Follow-up :9 mnths (18 on going)

Objectives

- To Compare mother breastfeeding (BF) under HAART With formula feeding (FF) for prevention of post natal HIV transmission
- To Determine pre and post- partum transmission rates
- To Determine the morbidity, mortality and developpement of the children according to the feeding mode

Methods: ARV

Eligible for HAART: CD4 < 350 or/and Stage 4 (WHO)

Continue HAART if already on treatment before 28 weeks of gestation or start **D4T +3TC + NVP** for life and choose feeding option before delivery

Non eligible: CD4 > 350 and Stage 1, 2, 3

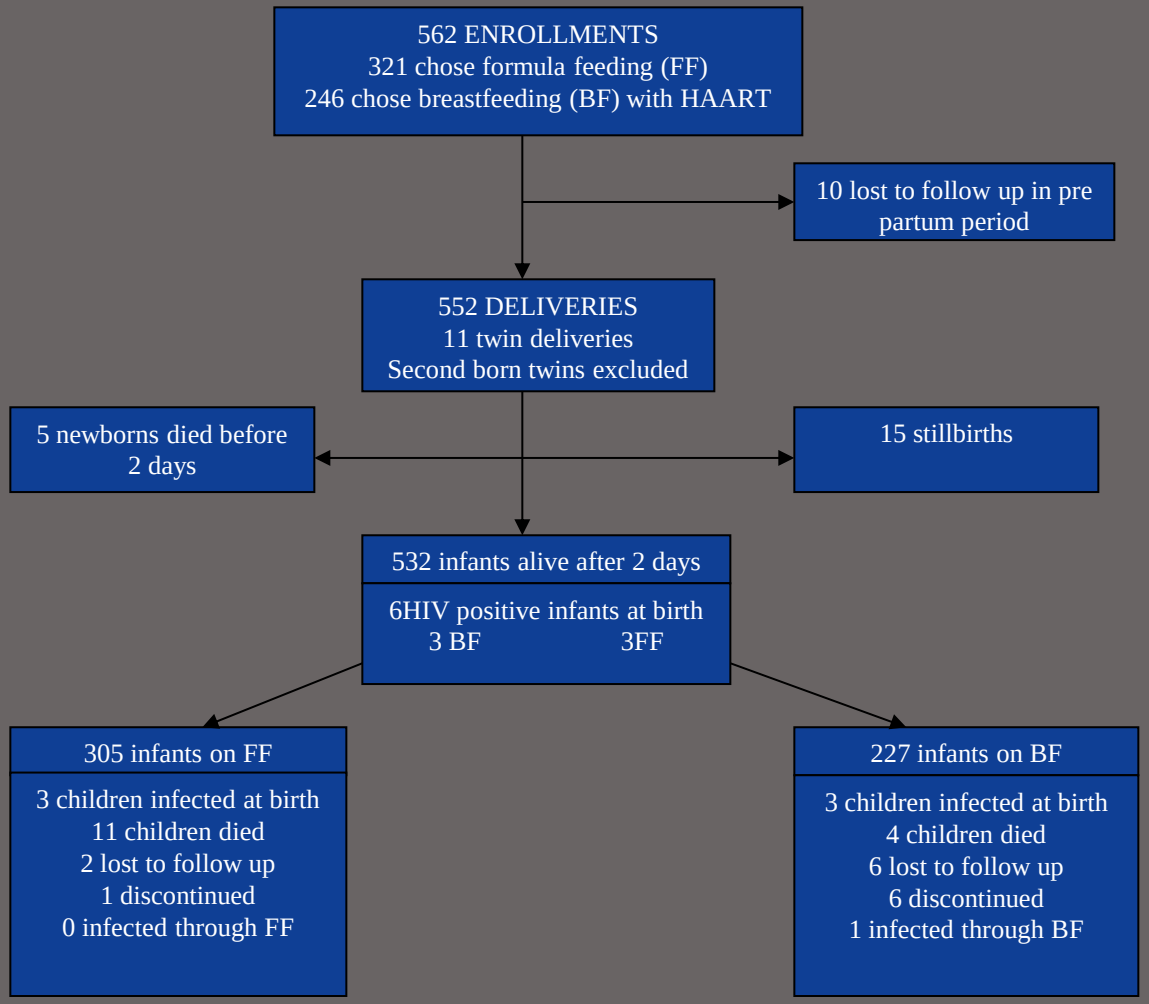
Start **AZT + 3 TC + Effavirenz*** from 28 weeks of gestation and choose feeding option before delivery

FF
Stop HAART** at birth.
Oestrodiol injection

BF
Exclusively until 6 months and stop HAART at 7 months.

All Newborn exposed to HIV: At birth: One dose of NVP: 2 mg/kg + AZT 4 mg/kg TID for 7 days

Résultats 1


562 ENROLLMENTS
321 chose formula feeding (FF)
246 chose breastfeeding (BF) with HAART
10 lost to follow up in pre partum period
552 DELIVERIES
11 twin deliveries
Second born twins excluded
5 newborns died before 2 days
15 stillbirths
532 infants alive after 2 days
6HIV positive infants at birth
3 BF 3FF
305 infants on FF
3 children infected at birth
11 children died
2 lost to follow up
1 discontinued
0 infected through FF
227 infants on BF
3 children infected at birth
4 children died
6 lost to follow up
6 discontinued
1 infected through BF

Résults:

- Transmission:
  - 6 (1,1%) infants infected at birth (PCR+ at Do)
  - 1(0,44%) infant infected through BF Between 3 and 7 months
  - Mothers plasma VL at delivery :

HIV-RNA copies/mL		
<40	40-1000	>1000
54,7%	35,7%	9,6%

Last documented TR in Rwanda:
25, 7 % * par rapporté par : *Am J Epidemiol.* 1993 Mar 15;137(6):589-99.

Résults:

- Mortality = 2,8 % at 7 months
- Mortality at 1 year : 11,6% in Rwanda
  - BF: 4 infants (1,9%)
  - FF : 11 infants (3,3%)

p=0,323 et RR=1,75 avec IC95%=[0,57-5,43]

Conclusions

-Very low rate of transmission and mortality in children breastfeeding 6 months from an HIV infected mother under HAART

-This allows early benefit of BF

- No significant differences between FF and BF children at 7 months

Essai MITRA PLUS : maintien d'une trithérapie chez la mère en post-partum + allaitement maternel

- 501 femmes dont l'infection par le VIH a été diagnostiquée au cours de la grossesse ont été incluses dans l'essai
- Tanzanie, avril 2004-juin 2006
- Traitement par ZDV + 3TC + NVP à partir du 3ème trimestre et jusqu'à 6 mois après l'accouchement
- Durée moyenne de l'allaitement maternel = 24 semaines

Allaitement maternel poursuivi	
• à 6 semaines	98 %
• à 3 mois	92 %
• à 4 mois	86 %
• à 5 mois	77 %
• à 6 mois	18 %

Taux de transmission du VIH à S6 : 4,1 % ; à M6 : 5,0 %

Kilewo C, IAS 2007, Abs. TUAX101

All HIV infected pregnant women should receive ARV therapy (EPF n= 4078)

	N	n	% VIH+	% PCR J0-J3
No treatment during pregnancy	120	18	15.0	4.9
- Trt per partum	58	8	13.8	5.6
- Not treated per partum	59	9	15.3	4.8
- Infant breastfeed	7	2	28.6	
treatment during pregnancy	3 958	77	1.9	0.9
- Treated per partum	3 598	50	1.4	0.9
- Not treated per partum	186	7	3.8	1.0
- Infant breastfeed	18	3	16.7	

Even with a mother low viral load at delivery: ARV therapy reduces MTC transmission

- **Meta Analysis of 7 European cohorts :**

Ioannidis JID 2001

- **1202 Mothers with VL <1000 copies (delivery)**
- **44 cases of transmission**
- **Under ARV : 1% (8/134; 95%CI 0.4-1.9%)**
- **No ARV : 9.8% (36/368; 95%CI 7-13.4%) p<0.001**

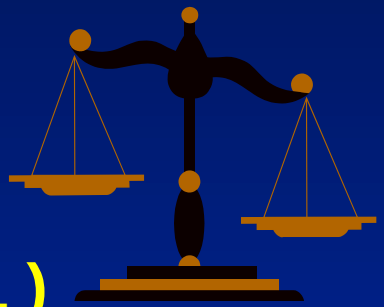
Multivariate A : ARV OR = O.1O; cesar prog OR = 0.3 et CD4 élevés OR = 0.39

EPF 1997- 2002

CV<1000 : 1921 treated : 0.83%

CV<1000 : 25 not treated : 8% p< 0.03

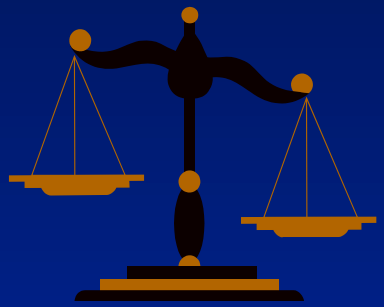
How to manage the HIV+ pregnant patient?



Maternal issues

- Adequate Rx (HAART/target bloq VL)
- Prevention of resistance
- Consider future options post partum

How to manage the HIV+ pregnant patient?



Maternal issues

- **Adequate Rx**
- **Prevention of resistance**
- **Consider future options post partum**

Infant issues

- **Minimise teratogens, And toxicities**
- **Minimise transmission risk**
- **protect her/his future**

Triple Therapy For Pregnant Women: Pre-Partum

- The Goal is to control the mother HIV/RNA load during the known moments of transmission
- Whatever regimen is used …

- The Answer to the question : Which regimen ? Would be : The one available at the moment… If potent , safe, accessible and not contra-indicated during pregnancy …

- In 2008 , The answer would be different according to:

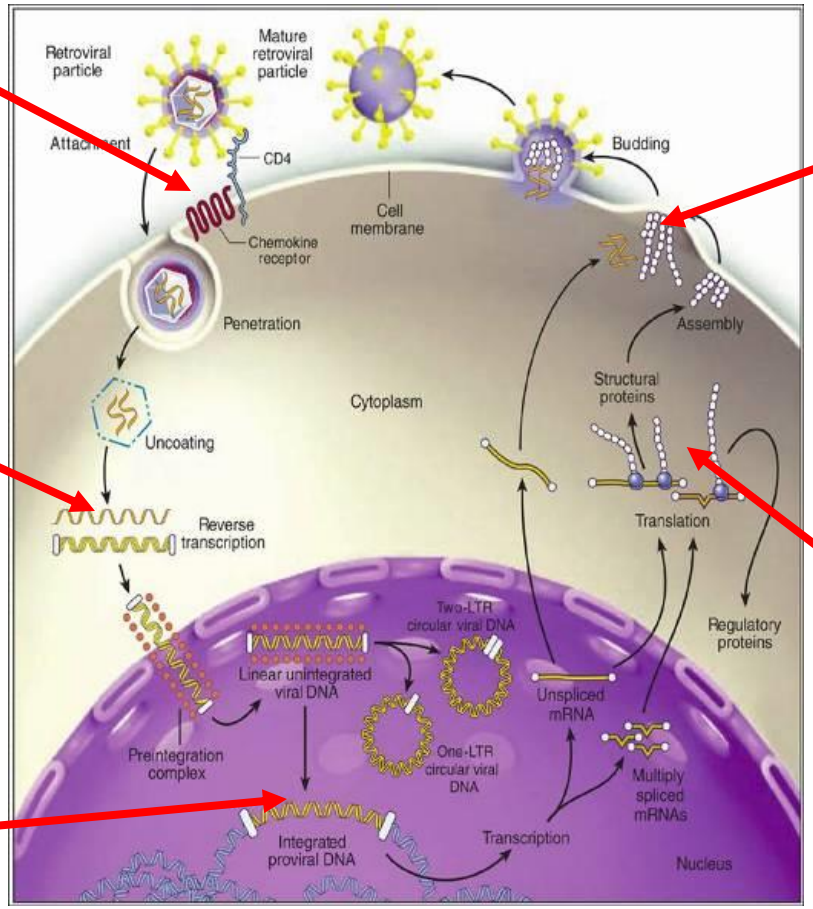
- National ARV programs
- Location within country (Access to HAART, lab capacity,ARV trained team..)
- Background of the women (resistance, adherence to the follow-up..)
- Others…

Which triple in 2008 ??

Entry inhibitors
ENF MRV
VCV TNX355
AMD11070

Reverse transcriptase inhibitors
ZDV NVP
ddI DLV
TDF EFV
d4T ABC
FTC 3TC
ETR RLP

Integrase inhibitors
EVT RAL
others



Protease inhibitors
SQV IDV
RTV NFV
FPV LPV
ATV TPV
DRV

Maturation inhibitor
bevirimat

Triple Therapy For Pregnant Women: Which Regimen ?

- 2 nucs + NNRTI :
- 2nucs + PI/r
- 3 nucs

- New Drugs : Integrase inhibitors or CCR5 inhibitors :missing data on pregnancy ..
- PI/r monotherapy : data pending (PRIMEVA study ANRS045)

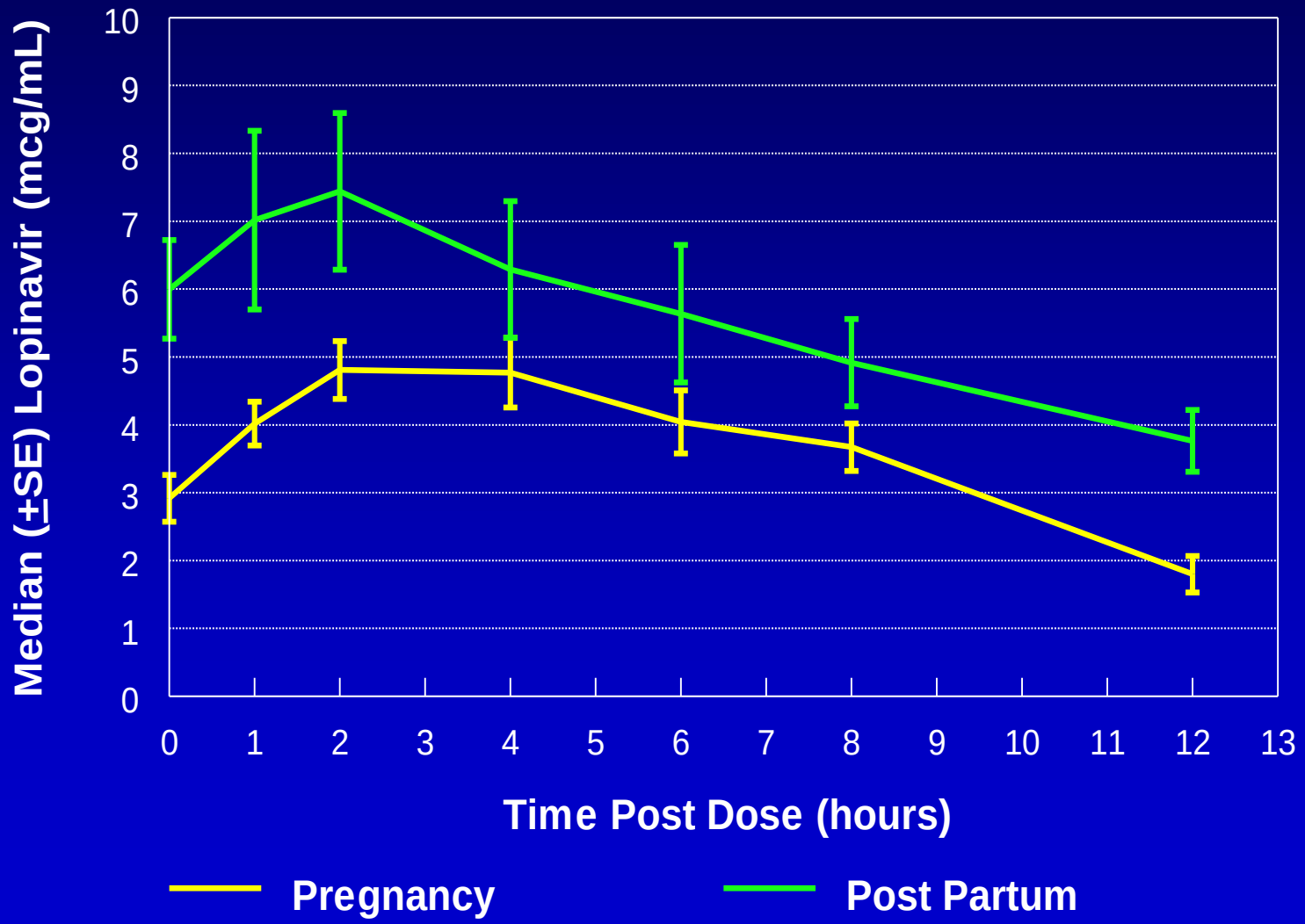
- **Pregnancy is not the best moment to start ARV therapy**

- **Short delay to be efficient , specific toxicities, issues for mother and children**
- **ARV should be initiated BEFORE the begining of the third trimester (28 weeks) for optimal reduction of MTCT**
- **Therefore , testing, evaluation and counselling should be performed at the 1rst or 2nd trimester**

Pregnancy is not the best moment to start ARV therapy

- Alteration of pharmacokinetics during pregnancy
  (use boosted PI)
- Pregnancy is a risk factor for Hyperglycemia and hyperlipidemia (monitor closely when PI administration)
- Lactic Acidosis and metabolic disorders as well as liver steatosis are known complications of pregancy (moniror closely when NRTI administration)

Lopinavir Plasma Concentrations
Pregnant (n=17) vs Post Partum (n=8)



Food and Drug Administration Pregnancy Categories

A : adequate and well controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk duging later trimesters

B : Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted

C : Safety in human pregnancy has not been determined ; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus

D : positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.

X : Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

Nucleoside and nucleotide analogues reverse transcriptase inhibitors

Antiretroviral drug	FDA pregnancy category	Placenta passage (newborn /mother drug ratio)	Long term animal carcinogenicy studies	Animal teratogen studies	Recommanded for use in pregnancy (human experience data)
Abacavir (Ziagen, ABC)	**C**	yes (rats)	pos (rats,mice)	POS	**Alternative** Hypersensitivity!
Didanosine (Videx, ddI)	**B**	yes	neg	neg	**Alternative** fatal lactic acidosis with stavudine
Emtricitabine (Emtriva, FTC)	**B**	unk	unk	neg	**Alternative** No study
Lamivudine (Epivir, 3TC)	**C**	yes	neg	neg	**YES**
Stavudine (Zérit, D4T)	**C**	yes	pos (rats high dose)	neg	**Alternative** fatal lactic acidosis with didanosine
Tenofovir DF Viread)	**B**	yes (rats, monkeys)	pos (rats high dose))	Neg (osteomalacia)	Insufisant data
Zalcitabine (HIVID, ddC)	**C**	yes	POS	POS	NO
Zidovudine (Rétrovir, AZT, ZDV)	**C**	yes	POS (rats vaginal tumors)	POS Rhodent near lethal dose	**YES** Based on efficacy and experience

Non-nucleoside reverse transcriptase inhibitors

Antiretroviral drug	FDA pregnancy category	Placenta passage (newborn :mother drug ratio)	Long term animal carcinogenicity studies	Animal teratogen sutdies	Recommanded For use in pregnancy (human experience data)
Devavirdine (Rescriptor)	**C**	unk	POS	POS	NO
Efavirenz (Sustiva,stocrin)	**D: 3 case reports of neural tube defect in humans**	YES (monkey,rat,rabbit) 1/1	POS (female rats)	POS : 3/20 monkey anencephaly anophtalmia, microphtalmia)	Not in first trimester and for women of childbearing potential
Névirapine (Viramune)	**C**	Yes (human) 1/1	**POS** (hepatocellular carcinomas mice and rats)	NEG (not performed in monkeys)	**YES if < 250 CD4** hepatotoxicity !! often rash associated (potentially fatal)

Antiretroviral drug: *Protease inhibitors*	FDA pregnancy category	Placenta passage (newborn: mother drug ratio)	Long term animal carcinogenicity studies	Animal teratogen sutdies	Recommanded For use in pregnancy (human experience data)
Amprenavir (Agenerase)	C	Unknown	**POS:** Hepatocellular Mice and Rats	**Deficient ossification** (rats, rabbits)	Insufficient Data To recommend use
Atazanavir (reyataz)	B	Unknown	**POS** Hepatocellular adenoma: Femal Mice and Rats	NEG	Insufficient Data To recommend use
Fosamprenavir (Lexiva)	C	Unknown	**POS** Hepatocellular	NEG	Insufficient Data To recommend use
Indinavir (Crixivan)	C	Minimal (not boosted)	**POS** Thyroid in male mice (highest dose)	NEG	**Alternative** To be used boosted with RTV: dose?
Lopinavir/r (Kaletra)	C	Unknown	**POS** Hepatocellular Mice and Rats	**NEG :** delayed ossification in rats at toxic doses	YES
Nelfinavir (Viracept)	B	Minimal	**POS** Thyroid in Rats	NEG	Stp
Ritonavir (Norvir)	B	Minimal	**POS** Hepatocellular Mice	NEG chryptorchidism in rodents	**Alternative** Low dose for boosting other PI
Saquinavir	B	Minimal	NEG	NEG	YES

No Evidence of Increase in Birth Defect Rate With Prenatal LPV/RTV

- Antiretroviral Pregnancy Registry: international, prospective, exposure-registration study
  - Sample size (N = 987) sufficient to detect 2.4-fold increased risk of birth defects in infants exposed to LPV/RTV
- No increased risk of birth defects
  - 2.4% (95% CI: 1.5% to 3.6%) birth defect rate comparable to 2.7% (95% CI: 1.6% to 4.1%) rate in general population
- Nonsignificant trend for association of exposure to LPV/RTV in the first trimester and increased likelihood of premature delivery, low birth weight
  - 13.4% of pregnancies lasted < 37 weeks
  - 19.2% of patients weighed < 2500 grams

Martinez M, et al. IAC 2008. Abstract TUPE0120.

Fusion inhibitors

Antiretroviral drug	FDA pregnancy category	Placenta passage (newborn :mother drug ratio)	Long term animal carcinogenicity studies	Animal teratogen sutdies	Recommanded For use in pregnancy (human experience data)
Enfurvirtide (Fuzeon)	**B**	**unknown**	**ND**	**NEG**	**Insufficient Data To recommend use**

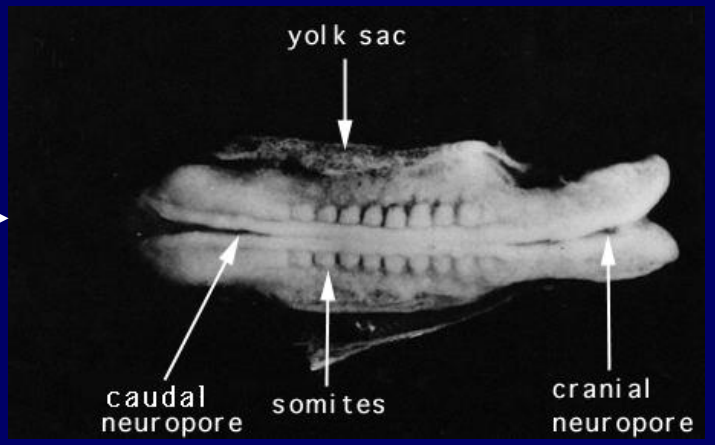
Potential for Teratogenicity with Efavirenz

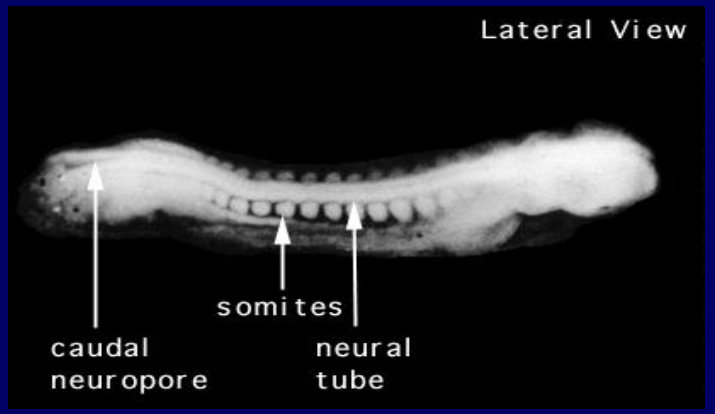
- EFV is teratogenic in primates at drug exposures equivalent to humans receiving therapeutic doses: 3/20 monkeys with anencephaly, an- or micro-ophthalmia.
- Human data:
  - Prospective reports from APR, 5 defects/206 pregnancies (2.4%), no pattern.
  - However, retrospective APR reports: 4 cases human infants with significant CNS defects with 1st trimester exposure (meningomyelocoele, Dandy-Walker).

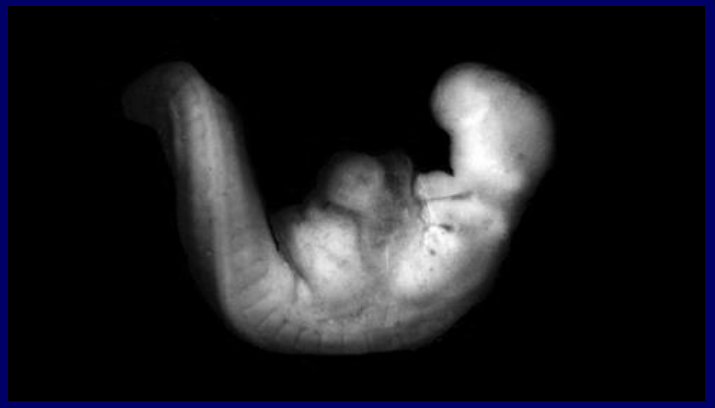
- In 2005, US FDA changed Pregnancy Classification to FDA Pregnancy Class D (positive evidence of human fetal risk).

Neural tube closure

- Day 22 - 23
- Day 23 - 26
- Day 26 – 30







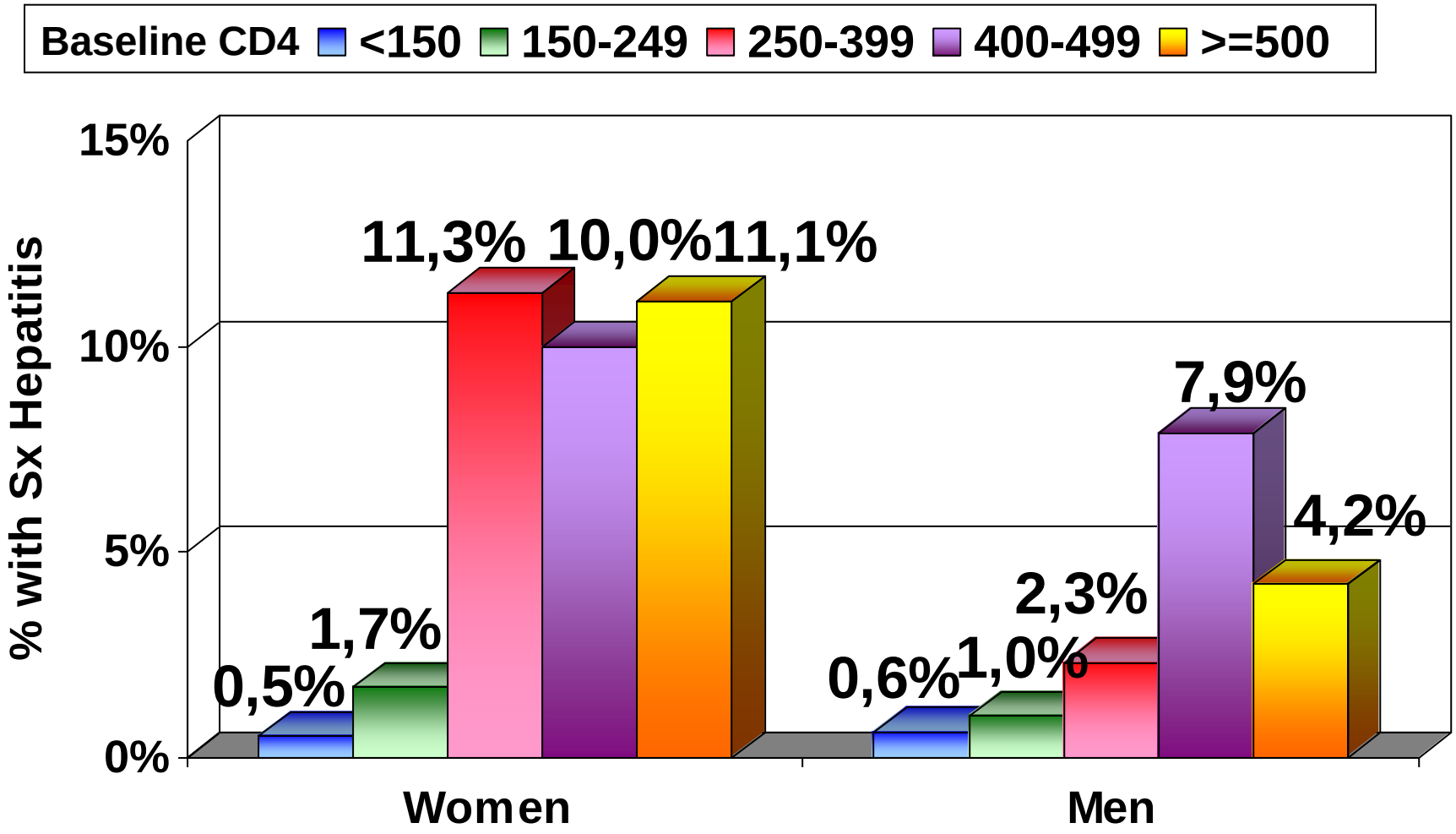
- Lateral edges of the neural folds meet in the midline to form the neural tube
- Fusion begins at the cervical end around day 22
- Process complete around day 26

NVP Toxicity Pregnant Women, U.S.: P1022

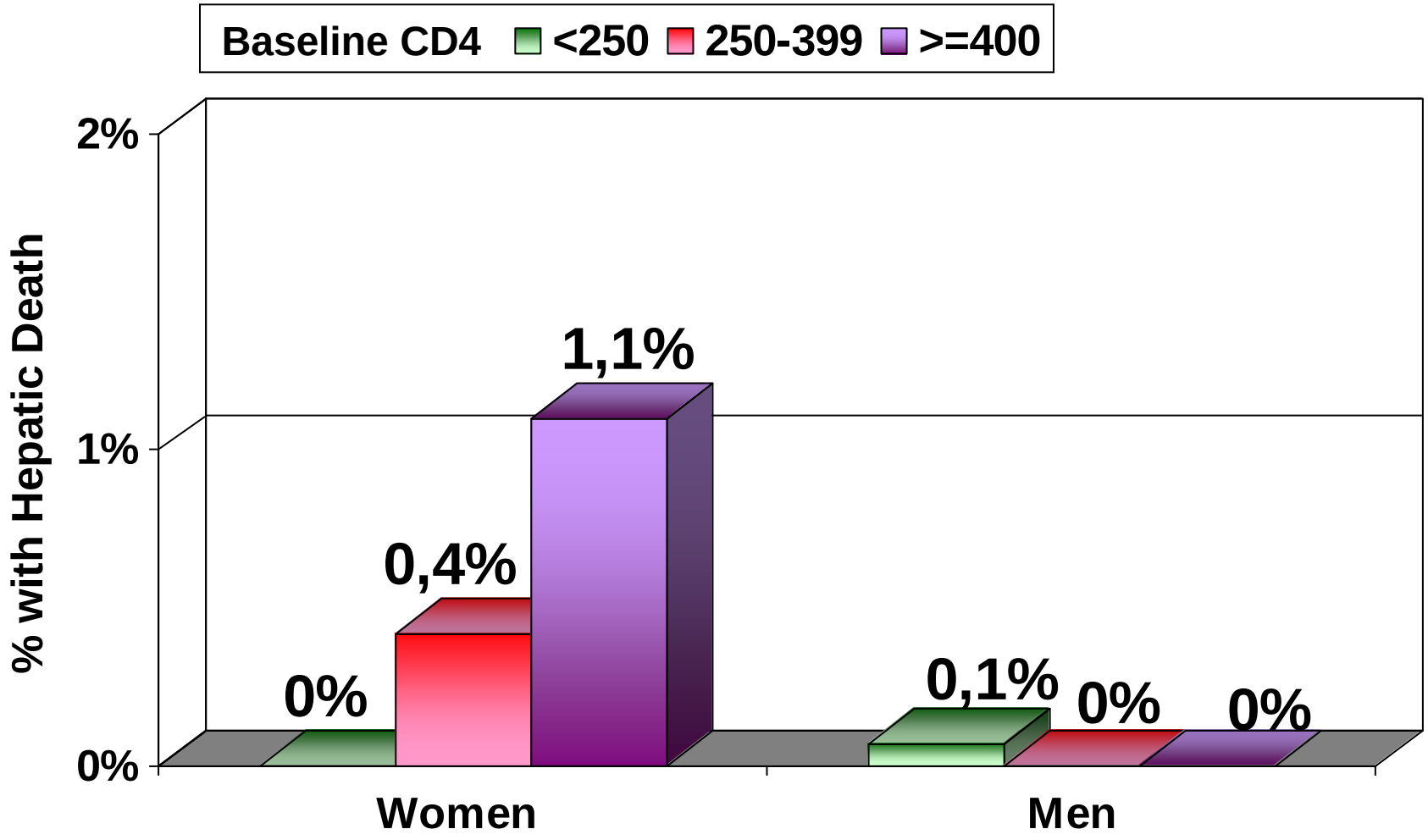
Hitti J et al. JAIDS 2004;36:772-6

- Compared AZT/3TC + NVP vs NFV in ARV-naïve pregnant women; stopped early.
- Treatment limiting toxicity seen in 1/21 (5%) NFV women and **5/17 (29%) NVP women**, including 1 hepatic death (14%).
- NVP arm: 53% black, 41% hispanic.
- Among women with CD4 >250, 0/14 receiving NFV had toxicity vs **5/14 (36%) receiving NVP**.
- NVP toxicity included SJS (1), increased ALT (2/3 symptomatic), fulminant hepatic failure and death despite stopping drug (1).
- All normal ALT entry and no HBV/HCV.

Symptomatic Hepatic Events in 1st 6 Weeks of NVP Therapy by Baseline CD4 Count and Gender (Boehringer-Ingelheim)



Fatal Acute Hepatic Events with NVP in Controlled Trials by Baseline CD4 Count and Gender (Boehringer-Ingelheim)



NVP and NFV Side Effects More Common in Pregnant than Non-Pregnant Women?

Timmermans S et al. AIDS 2005;19:795-9

Compared toxicity in 186 pregnant and 186 non-pregnant Dutch HIV-infected women from 15 centers.

	Nevirapine			Nelfinavir		
Side effect	Non-Preg **(N=95)**	Preg **(N=58)**	**P value**	Non-Preg **(N=91)**	Preg **(N=128)**	**P value**
GI	5%	9%	0.42	7%	30%	0.001
Rash	11%	9%	0.70	1%	1%	0.80
Hepatitis	4%	19%	0.003	4%	4%	0.86
↑ Glucose	1%	9%	0.02	2%	16%	0.001

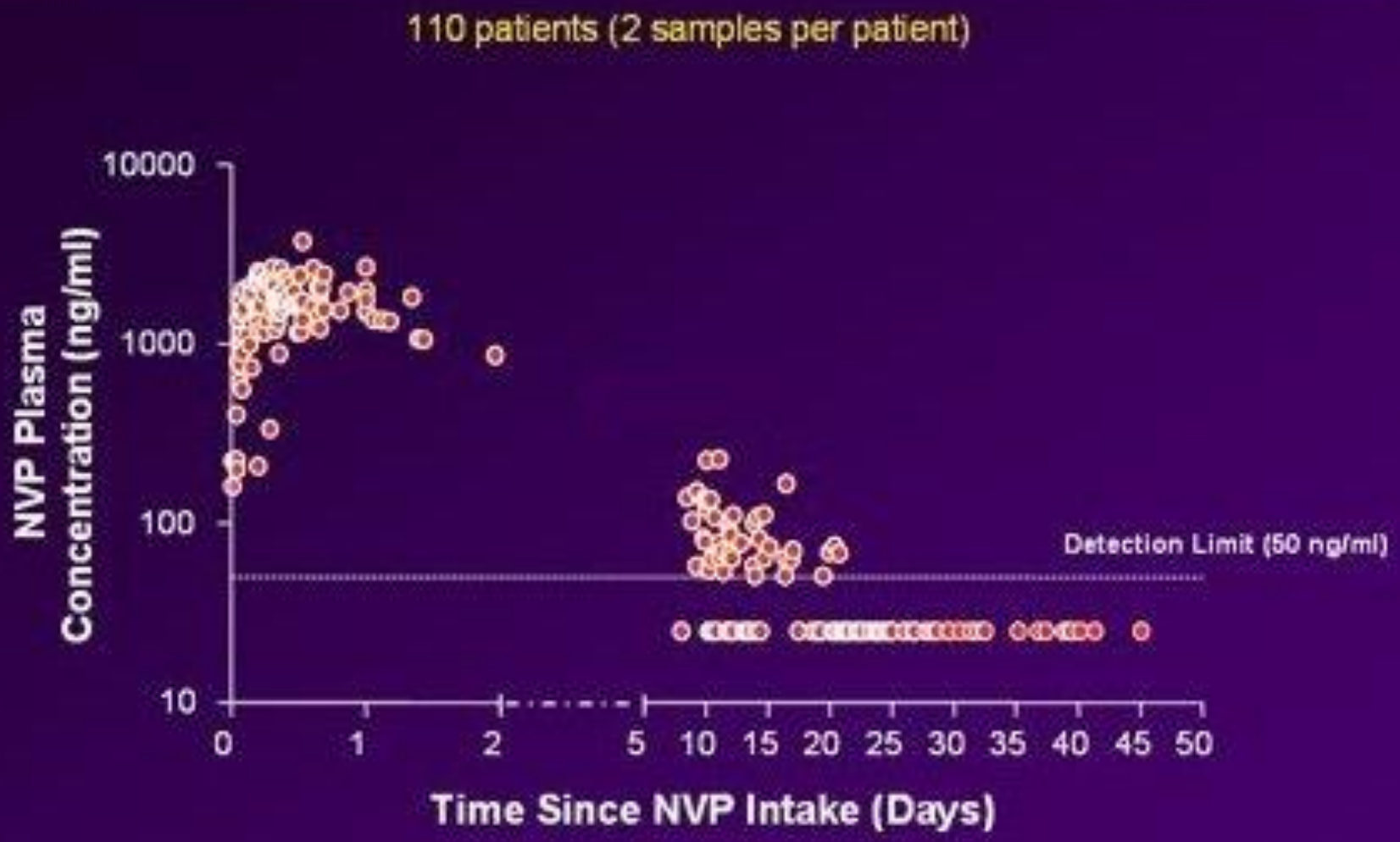
Is nevirapine mandatory in the context of prevention of HIV-1 MTCT?

- Monotherapy is less effective than HAART++
- Toxicity to be monitored closely if the future mother is >250 CD4
- Resistance is an issue if you stop NVP at delivery or use SD
- **SD NVP in mother and child is a salvage therapy if no other choice is available but is sub-optimal to Prevent MTCT +++**

- **To avoid selection of resistant strains and optimise mother and child protection :**

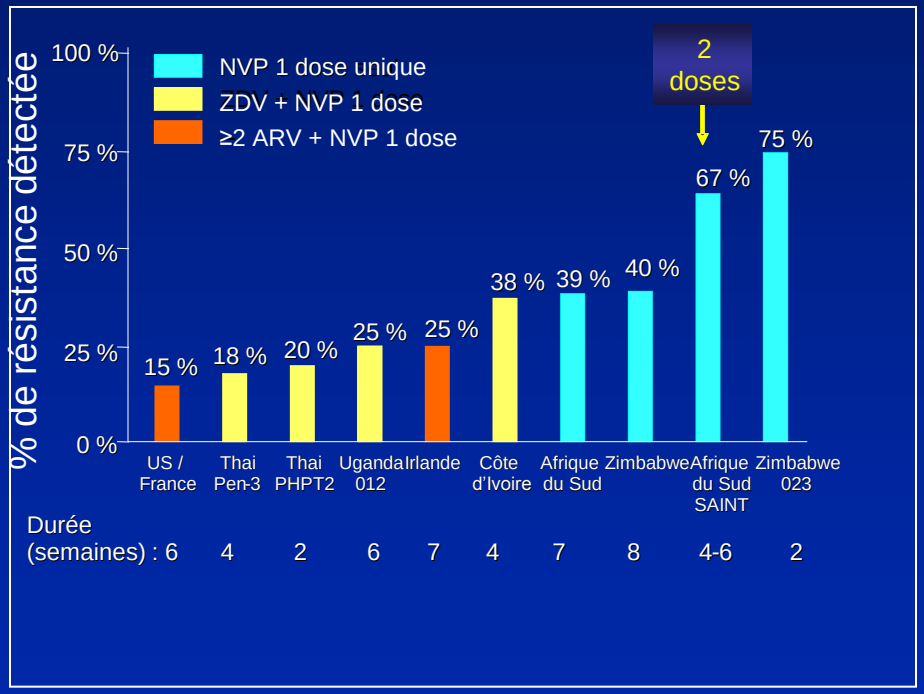
  NVP should be used as a component of combination regimen, not stopped after delivery if the women status recommend ARV or if she plans breastfeeding.
- If the treatment is interrupted ,continue with the other drugs of the combination **a** for at least a week **(2)**
- **The use of HAART ,including 2 NUCS+a boosted PI should be considered in this indication ++**

PHPT-2 NVP Plasma Drug Levels

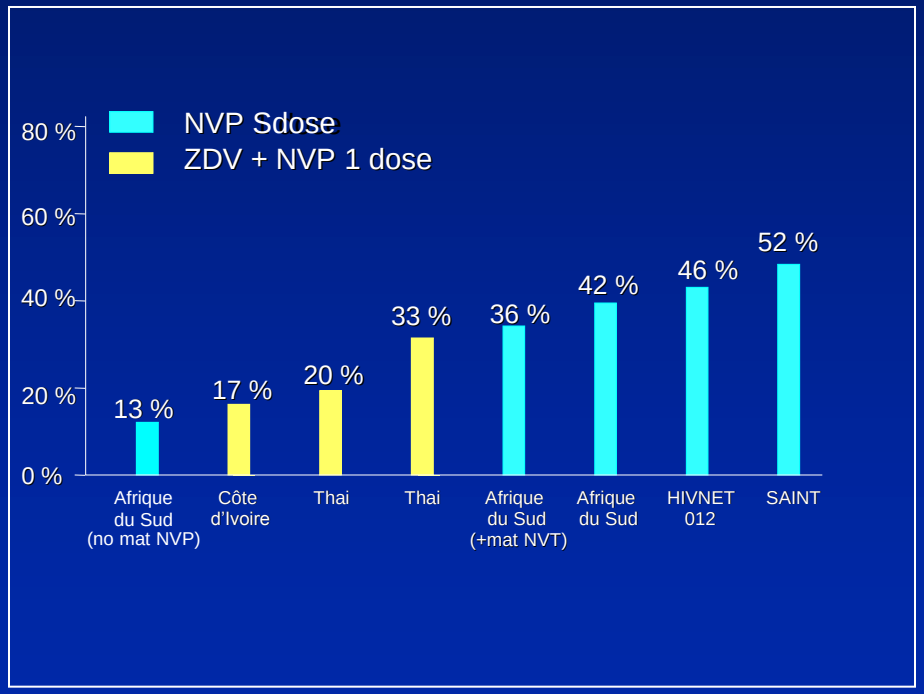


Acknowledgements: Tim Cressey, PHPT, Bangkok 2004

Acquisition of résistance to NVP after1 dose In mothers



Acquisition of résistance to NVP after 1 dose in babies



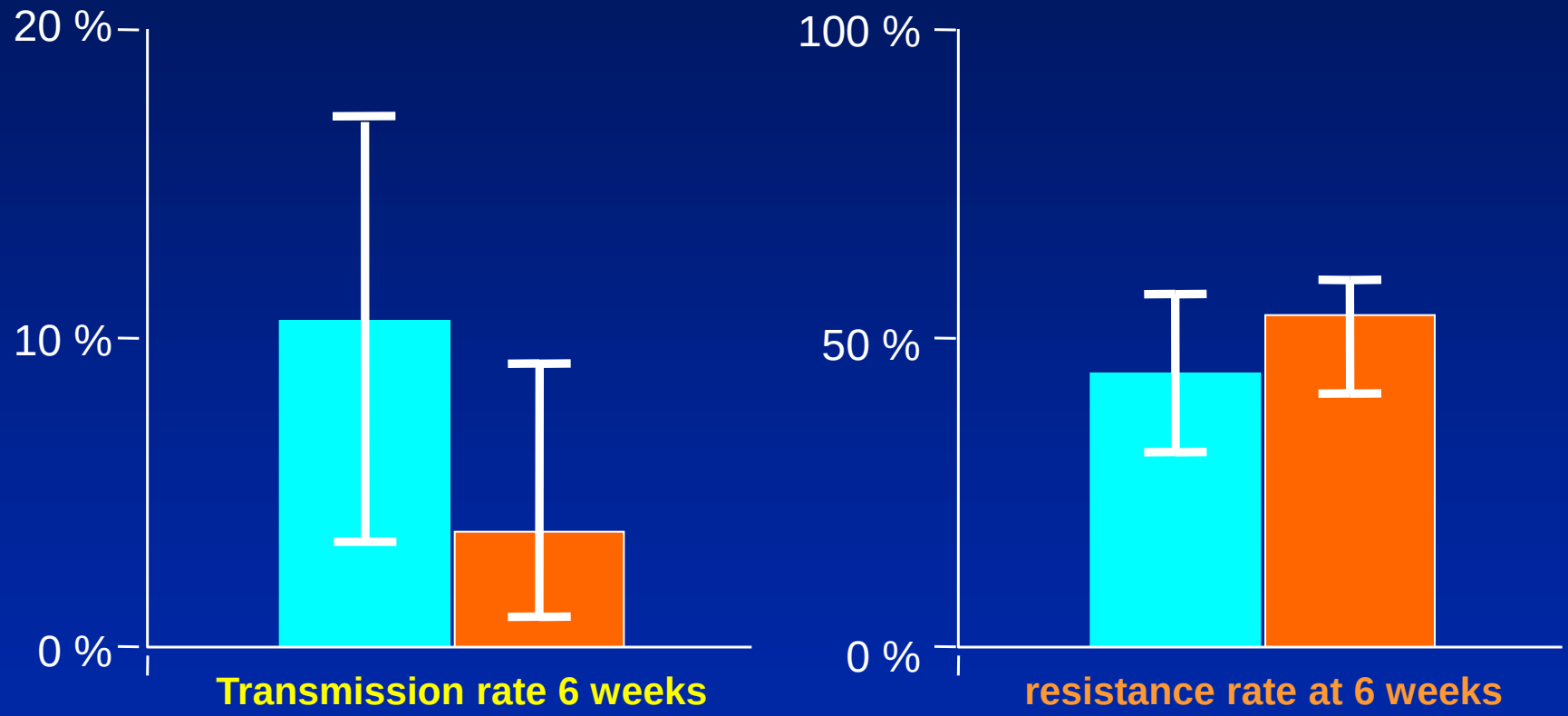
McIntyre J., CROI 2005, Abs. 8

Resistance

-What is the clinical significance of the resistance mutations (detected/or not detected)? Will it jeopardize future treatment options for women and infants?

Strategies to minimize resistance mutation taking into account efficacy, toxicity, tolerance, adherence, and cost of preventive and therapeutic supressive strategies

Efficacy of NVP single dose during second pregnancy



Martinson N., CROI 2005, Abs. 103

Tenofovir and Developmental Bone Toxicity

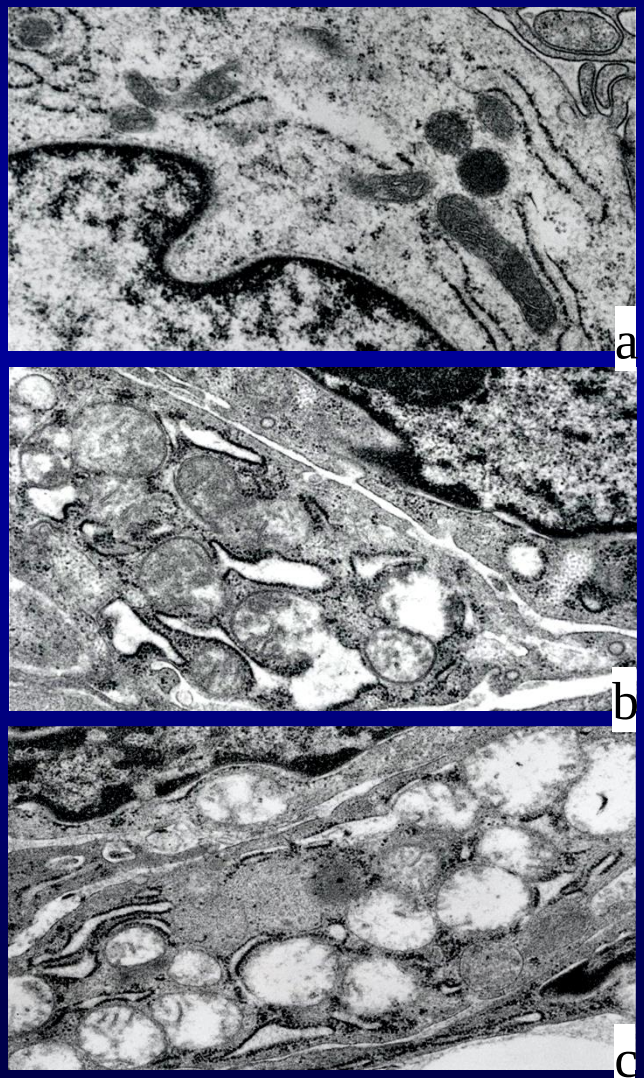
- Fetus (*Tarantal. JAIDS 1999;20:323-33):* Bone marker/ density changes in primate fetuses with *in utero* exposure ~25x > than human exposure:
  - No gross congenital abnormalities.
  - Significantly lower fetal insulin-like growth factor-1 (regulator linear growth), high BP-3.
  - Reduction fetal bone porosity.
- Chronic TFV in immature animals of multiple species results in reversible bone changes; is dose-, exposure-, age-, species-specific.
- Unknown effect with human fetal exposure; 1 defect (renal)/96 1st trimester exposure (APR).
- Ped Rx (*Gafni. Pediatr Res 2004;55:329A, abs 1873):* ARV-experienced children 6-16 yrs; baseline BMD < normal, decrease with 24 wks TFV.

Possible Mitochondrial Dysfunction and Perinatal Exposure to Nucleoside Analogues

Blanche. Lancet 1999;354:1084-9; Barrett. AIDS 2003;17:1769-85; French Perinatal Cohort Study Grp. Lancet 2002;359:583-4;

- French Perinatal Cohort has reported 12 cases (2 deaths) mitochondrial dysfunction in cohort of 2,644 uninfected children with ARV exposure.
  - Primarily neurologic symptoms
  - May have hyperlactatemia
  - Abnormalities respiratory chain function
- 18 mo incidence 0.26% (95% CI, 0.10-0.54%).
- 18 mo mortality 0.07% (2 of 2,644).
- Also reported elevated risk of first febrile seizure in uninfected ARV-exposed children.

Mitochondrial damage by EM in endothelial cells of umbilical artery



R. Divi AIDS 2004

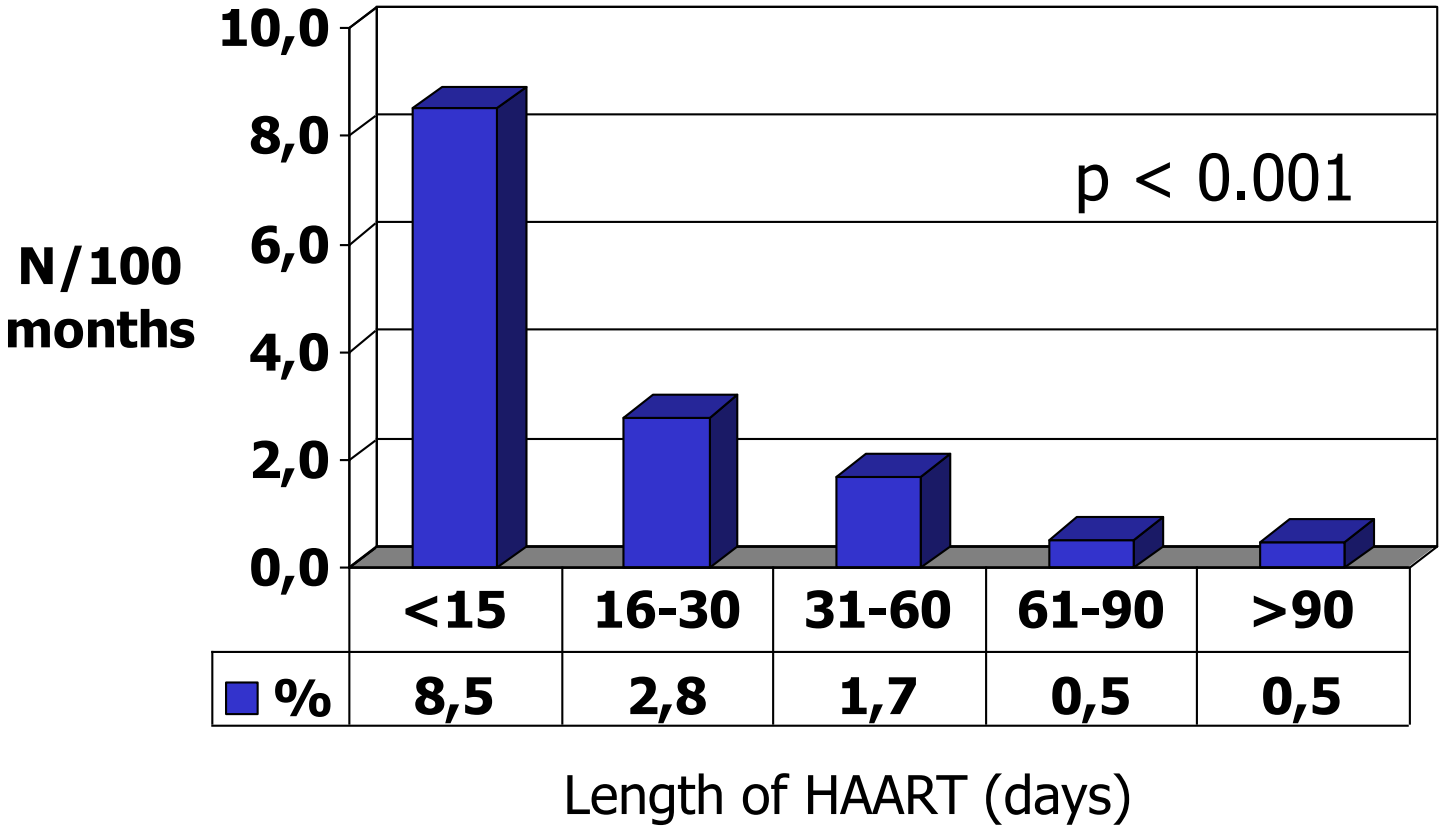
	Unexposed	AZT+3TC
Normal	6	2
Mild	1	1
Moderate to Severe	0	6

Adverse Pregnancy Outcome and HAART

- Controversial if HAART associated with pre-term delivery; data differ US and Europe.
- *Lorenzi (AIDS 1998;12:F241-7):* Swiss, N=30

  33% preterm in women on combo ARV.
- *ECS (AIDS 2000;14:2913):* Europe, N=2,819
  - OR 2.6 preterm if combo PI, 1.8 if combo no PI vs no ARV; no increase with 1 ARV.
  - Risk highest if combo ARV started pre-pregnancy than if started 2nd/3rd trimester.
- *Tuomala (NEJM 2002:346:1863):* US, N=1,143
- *Tuomala (JAIDS 2005;38:449-73):* US, N=2,543
  - No increase preterm with PI or combo.

- Abortion and Stillbirth cumulative number per 100 observation months according to the length of pre-delivery HAART (1223 deliveries)



the DREAM Program
2006 Mozambique

Guidelines for HIV+Pregnant Women

- Provide standard clinical evaluation- HIV disease stage
- Evaluate degree of immunodeficiency- CD4 cell count, %
- Assess risk of disease progression as determined by level of plasma HIV-RNA
- Document history of prior or current ARV use
- Perform drug resistance testing
- Discuss known or unknown risks/benefits of therapy during pregnancy
- Develop strategy for long term evaluation and management of mother and infant

Comprehensive and multidisciplinary follow-up

- Testing for future mother (and father) ++
- Counselling and therapeutic options
- Infectious and obstetrical follow-up
- Mode of delivery
- Infant prophylaxis
- post-partum mother care
- Follow up of the baby
-
  - Psychological issues
  - Social issues
  - Family and relative confidentiality
  - Infectious issues
  - future pregnancies

French recommendations :2008

- **Objective**: undetectable plasma Viral load
- **From26 weeks until delivery** (earlier if risk of prematurity)
- AZT monotherapy is not generally recommanded
- Warning on **névirapine initiation** during pregnancy Severe Liver Toxicity and toxidermia reported in women > 250CD4) and **triple nucs** (efficacy and mitochondrial toxicity.)

  The recommanded HAART is **2 NUCS+PI**

Elective CS is not recommanded if plasma VL is undetectable at 36weeks , exept if bad adherence , tolérance , low CD4 or obstetrical indication

French recommendations :2008

Scenario 1:**Women currently on antiretroviral therapy**

- **If viral load BLQ and CD4>200 : continue treatment**
- **Exept : EFV, D4T+DDI, 3 nucs, (few data on abacavir and tenofovir)**
- **If viral load detectable: to be modified according to therap history, toxicities, adherence, eventually resistance testing with respect- to pregnancy specificity**

French recommendations :2008

Clinical Scenario 2

Women without prior antiretroviral therapy

- **If CD4<350 : start 2 Nucs+PI, if possible after 12 and before 26 weeks ..**
- **The choice is usually AZT+3TC + Boosted PI (cf)**
- **If CD4> 350 :same treatment initiated from 26 weeks…**
- **Always assess efficacy, toxicities , tolerance , compliance...**

French recommendations :2008

Scenario 3: **late diagnosis or late presentation**

- **Rapid testing and specific counselling to parents**
- **>8months gestation and before delivery:**

start HAART 2N+PI + Planified ECS , and if necessary NVP single dose at delivery. Treat the new born with multitherapy for 6 weeks.

Social and psychological care and support very often necessary

- **During labour :**

AZT infusion and Single dose nevirapine for mother at onset of labor followed by single dose of nevirapine for the newborn at 48–72 hrs of age

and re-enforce the new born treatment

French recommendations :2008

DELIVERY

- Intrapartum IV ZDV recommanded in all cases
- Schedule CS at 38-39 weeks not mandatory if the mother viral load is undetectable at 36 weeks

….. Exept in case of

- Obstetrical indication, mono AZT, detectable VL at 36 SA , CD4 < 200 , mother's decision…..
  - Stress importance of adherence to therapy before delivery

Intrapartum IV AZT

- AZT 2mg/Kg iv over 1 hour, then 1mg/Kg/hr until delivery.
- Start treatment at the onset of labour. Or 4 hours before C section
- Treatment to continue during C.Section until delivery.

French recommendations :2008

infant

- Antiseptic bath at delivery
- No breast-feeding
- ARV prophylaxis : Azt for 4 weeks , multiple therapy 6 weeks if mother harbouring resistant strains or not under efficient therapy or late presenter. .
- Follow up by experimented pediatricians : HIV-PCR testing , tolérance and toxicity of ARV therapy (anemia with AZT) and clinical until 24 months ..

Solthis
SOLIDARITÉ THÉRAPEUTIQUE & INITIATIVES CONTRE LE SIDA

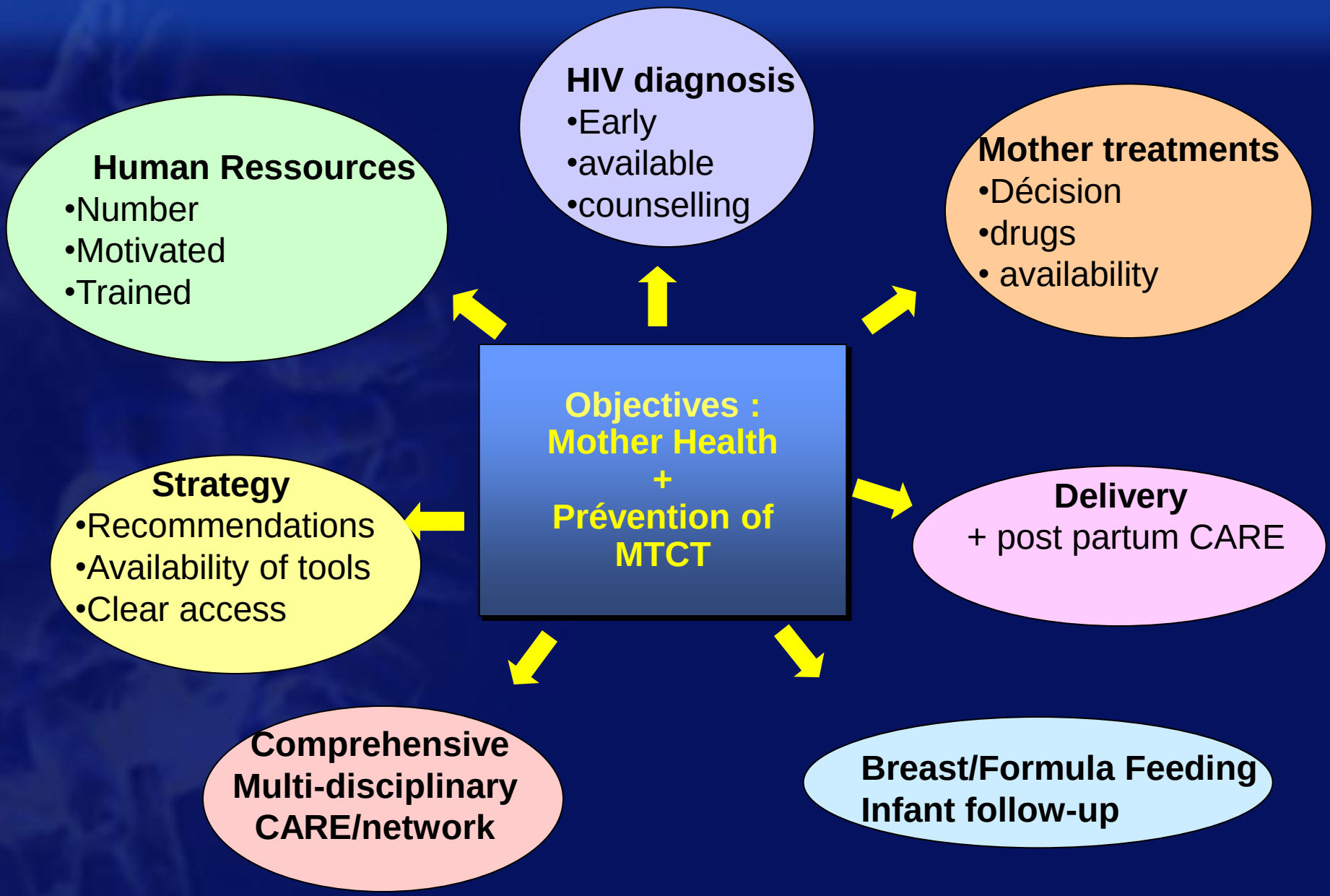
PMTCT national guidelines

	MALI (under revision)	NIGER
Mother		
-HAART ongoing	Change EFV to NVP or IP/r	Idem
- HAART indication	**WHOIII/IV and/or CD4 <350** **Accredited centre: HAART**(*) as soon as possible If not, AZT/3TC (>28W) +sdNVP +AZT/3TC 14days	**WHOIII/IV and/or CD4 <250** **Accredited centre: HAART** as soon as possible If not, AZT(>28W) +sdNVP +AZT 14days
- No HAART indication	**WHOI/II and/or CD4 >350** **Accredited centre: HAART**(*) >28W If not, AZT/3TC (>28W) +sdNVP +AZT/3TC 14day	**WHOI/II and/or CD4 >250** AZT (>28W) +sdNVP +AZT/3TC 14day
- Late diagnosis (> 36W)	AZT/3TC+sdNVP +/- AZT intrapartum + AZT/3TC 14day	AZT +sdNVP +/- AZT intrapartum + AZT 14day
Newborn	**Mother complete prophylaxis** sdNVP + AZT 2W **Mother incomplete or any prophylaxis** sdNVP + AZT/3TC 4W	**Mother had > 4W ARV prohylaxis** AZT 4W **All other cases** sdNVP + AZT 2W
Breastfeeding	Replacement feeding	Replacement feeding or exclusive breastfeeding 6 months

(*) AZT(d4T)-3TC + NVP or LPV/R or IDV/r or SQV/r or ATV/r

Others GOALS

- To reach rural populations and women who deliver at home,
- Increase male involvement in PMTCT
- Do not separate PMTCT and HIV care for women …
- scale-up of PMTCT is possible in resource-limited settings, but mobilisation of key stakeholders and political will is essential


HIV diagnosis
•Early
•available
•counselling
Human Ressources
•Number
•Motivated
•Trained
Mother treatments
•Décision
•drugs
• availability
Objectives :
Mother Health
+
Prévention of
MTCT
Strategy
•Recommendations
•Availability of tools
•Clear access
Delivery
+ post partum CARE
Comprehensive
Multi-disciplinary
CARE/network
Breast/Formula Feeding
Infant follow-up

Conclusion

- A dramatic reduction of MTCT is achievable when access to global recommended care on time
- The use of nevirapine single dose in many PMTCT programms in the world may increase the spread of resitant strains in countries were the more affordable therapy contains NNRTI.. (to treat the mother after delivery could be the solution …)
- Because ARV therapy changes fast, standard care are difficult to establish: ex:More HAART and less CS
- Safety data lacking for most ARV
- Need for further evaluation of PI-based regimens, particularly in resource-poor settings
- Consider research on novel strategies for prevention of mother-child transmission with increasing safety for both……

Triple therapy in pregnancy could be the right answer for mothers and children in Africa