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# *HIV in pregnancy*

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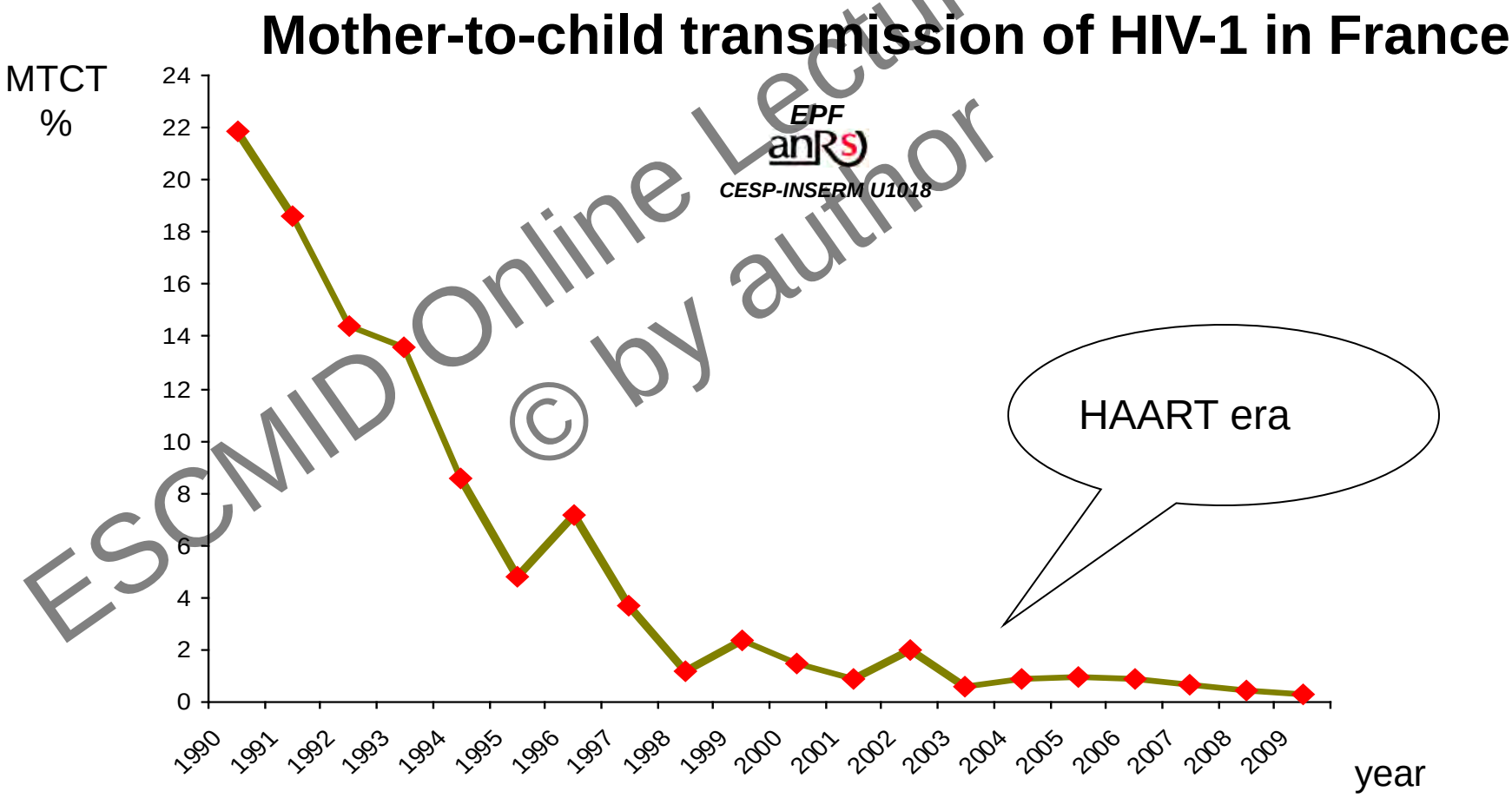
# *"PMTCT" : a success story*



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COUNTDOWN TO **ZERO**

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Do it.

Born HIV Free



# GLOBAL PLAN TOWARDS THE ELIMINATION OF NEW HIV INFECTIONS AMONG CHILDREN BY 2015 AND KEEPING THEIR MOTHERS ALIVE

2011-2015

2011-2015

# *HIV testing and counseling and pregnancy : recommendations*

- Preconception whenever possible
- 1st trimester of pregnancy : universal with « opt out »
- Offer test to partners
- Repeat testing (6th month of pregnancy) in case of risk factor : HIV+ partner, multiple partners
- Rapid testing in labor for women not screened during the pregnancy

# *HIV in pregnancy concerns both for the mother and the unborn child*

Who should be treated with ARV ?

Classically :

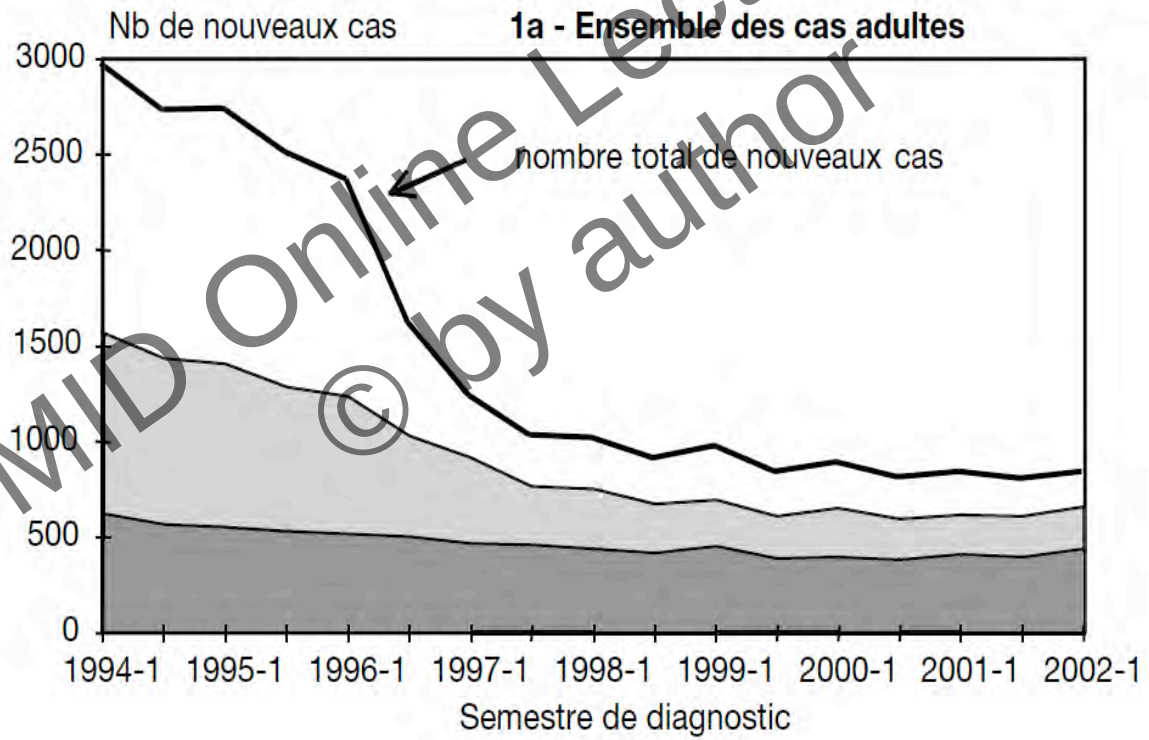
- Adults with CD4 count < 500
- Prevention of mother-to-child transmission (PMTCT) always

In 2013 :

- Lifelong ARV for all HIV+ persons ?

Objective : undetectable viral load

# *Spectacular improved outcome in HIV-infected persons with antiretroviral therapy*




Incidence of AIDS declined 10-fold in the cART era : most cases in people who were unaware of being HIV+

# *HIV and pregnancy : what are the issues in 2103 ?*

- When to start ARV ?
- What ARV to use ?
- Obstetrical care : C-section, intravenous intrapartum AZT
- Neonatal prophylaxis : what to use, how long ?
- Breasfeeding : can it be safe ?
- Should ARV be stopped in the mother after delivery ? (no)

# MTCT of HIV-1 according to time of maternal therapy and viral load at delivery

| Viral load at delivery | Time at initiation of cART during pregnancy: before conception | | 1st trim ≤14 WG | | 2nd trim 14-27 WG | | 3rd trim ≥28 WG | | |
|---|---|---|---|---|---|---|---|---|---|
| | % | n/N | % | n/N | % | n/N | % | n/N | p |
| CV > 400 cp/mL | 2.0 | 7/ 346 | 1.2 | 1/ 86 | 1.6 | 6/ 365 | 3.7 | 9/ 241 | |
| 50 - 400 cp/mL | 0.21 | 1/ 474 | 1.03 | 1/ 97 | 1.47 | 9/ 610 | 2.87 | 9/ 314 | |
| CV <50 cp/mL | 0.0 | 0/ 2259 | 0.25 | 1/ 399 | 0.60 | 8/ 1503 | 0.50 | 2/ 400 | 0.004 |

2000-2010, n=7094

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# *ART and pregnancy challenge*

Residual MTCT

Safety

# *Persistant toxicities of perinatal exposure to NRTI zidovudine and lamivudine*

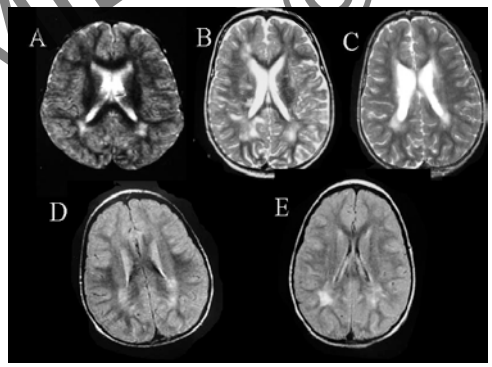
- **Hematopoietic, neurological or myocardial symptoms in children**

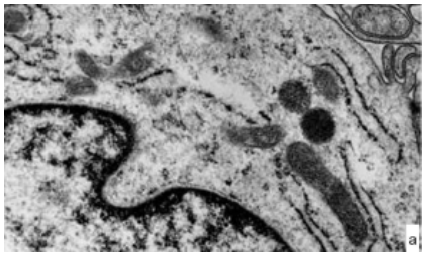
  *(Blanche 1999, Barret 2002, Le Chenadec 2003, Noguera 3003, ECS 2004, Pacheco 2006, Brogly 2007, Brogly 2011, Lipshulz 2011)*

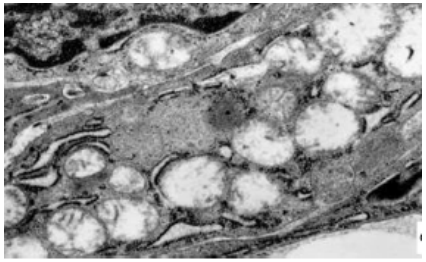
- **Fetal mitochondrial and genotoxicity in rodents, monkeys and humans**

  *(Divi 2004, Blanche 2006, Olivero 2008, Côte 2008)*





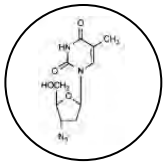


**Unexposed** **Exposed**

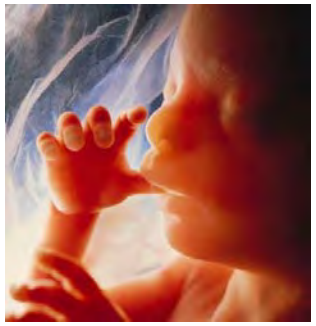
Mitochondrial depletion in cord tissue of neonates exposed in utero to Combivir *(Divi et al. AIDS 2004)*

# *Impact of AZT on nuclear DNA ?*

**Mitochondrial DNA**
**Nuclear DNA**

3'-azido-3'deoxy-thymidine



- Mice
  - AZT-DNA in many organs at birth
  - Mutations at 15 days
  - Shortened telomeres
  - Tumors in young adulthood
- Monkeys
  - Drug-DNA incorporation at birth
  - Shortened telomeres
  - Micronucleus
  - Supernumerary centrosomes
- Newborn infants
  - AZT-DNA incorporation
  - Hematopoietic stem cell CD34+ genotoxic alteration
  - Mutations

# *Antiretroviral drugs in pregnancy : what are the risks ?*

***For the fetus***

- **Malformations**
- **Hematologic toxicity**
- **Mitochondrial disease**
- **Preterm birth**

***For the mother***

- **As in non-pregnant persons**
- **Susceptibility to elevated liver enzymes**

***Long-term risks for infant***

- **Bone, kidney ?**
- **Cancers ?**
- **Accelerated aging ?**
- **Autistic disorders ?**

# *HIV and pregnancy : what are the issues in 2103 ?*

- When to start ARV ?
- What ARV to use ?
- Obstetrical care : C-section, intravenous intrapartum AZT
- Neonatal prophylaxis : what to use, how long ?
- Breasfeeding : can it be safe ?
- Should ARV be stopped in the mother after delivery ? (no)

# *ARV : when to start ?*

- As early as possible, taking into account :
  - Indication for the mother (never an emergency) : low CD4, symptoms
  - High viral load (HIV-1 RNA)
  - Preterm delivery risk
- PMTCT in all cases starting at 14 weeks, with consideration of deferring in selected cases (26 wks)

# MTCTC is higher when maternal ARV duration is shorter

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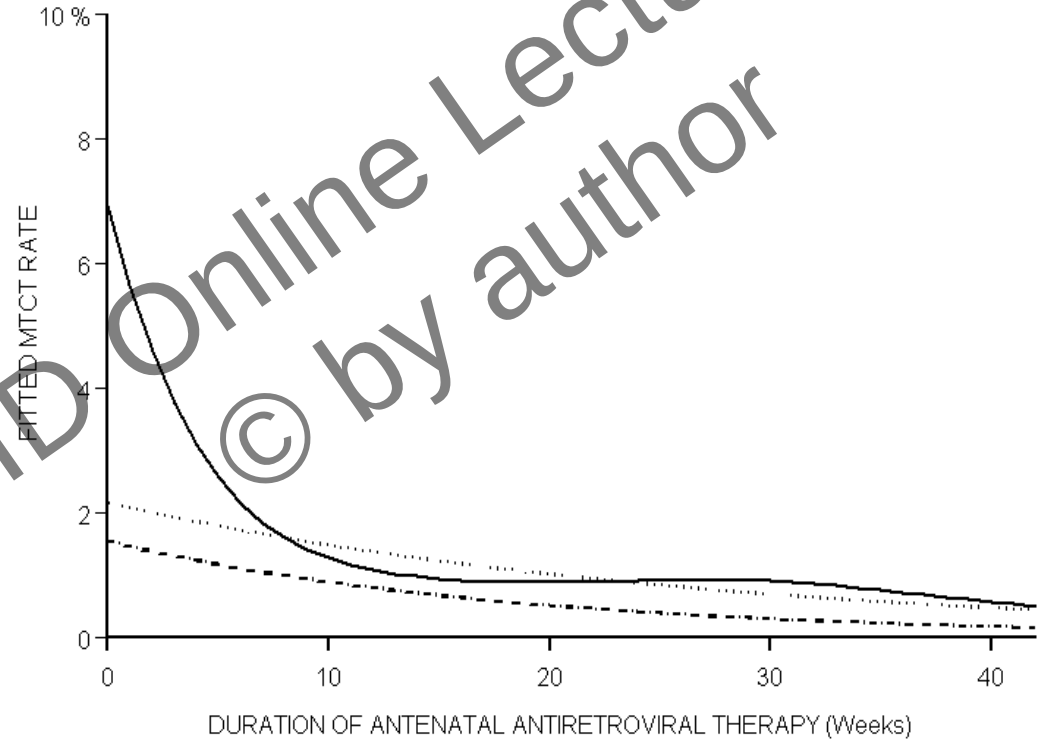


*Warszawski et al AIDS 2008*

# *What ARV to use ?*
# *Clinical scenarios*

1) Woman HIV-1+ not on therapy

2) Woman HIV-1+ starting pregnancy on therapy

3) Late presenter

4) Special cases

# Antiretrovirals available in 2013

## Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Zidovudine AZT (Retrovir)
Lamivudine 3TC (Epivir)
Abacavir ABC (Ziagen)
Tenofovir TDF (Viread)
Emtricitabine FTC (Emtriva)

AZT+3TC (Combivir)
ABC+3TC (Kivexa)
TDF+FTC (Truvada)

## Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Nevirapine (Viramune)
Efavirenz (Sustiva)
Etravirine (Intelence)
Rilpivirine (Edurant)

## Entry Inhibitors

Enfuvirtide (Fuzeon) – Fusion Inhibitor
Maraviroc (Celsentri)– CCR5 Inhibitor

## Protease Inhibitors (PI)

Lopinavir/ritonavir (Kaletra)
Atazanavir (Reyataz)
Darunavir (Prezista)

Ritonavir (Norvir) : “boost”

## Integrase Inhibitors

Raltegravir (Isentress)
Dolutegravir
Elitegravir

## Fixed combinations

Sustiva/Truvada (Atripla)
Tenofovir/FTC/rilpivirine/(Eviplera)

# HIV-1+ pregnant woman presenting without therapy

| 2 NRTI | | |
|---|---|---|
| **Zidovudine + Lamivudine**<br><br>Historical treatment<br>Wide experience<br>Mitochondrial toxicity | **Tenofovir + Emtricitabine**<br><br>First line outside pregnancy<br>Less mitochondrial tox<br>Lack long term safety data | **Abacavir + Lamivudine**<br><br>HLA-B*5701 testing<br>Lack long term safety data |
| **+ 1 PI boosted with ritonavir** | | |
| **Lopinavir**<br><br>Most data and experience | **Atazanavir**<br><br>Pregnancy mentioned in licence | **Darunavir**<br><br>Fewer data<br>Good tolerance |

- **Alternatives : 2 NRTI + efavirenz from 2d trimester (despite few data)**
- **Avoid :**
  - **efavirenz in 1st trimester (malformation risk)**
  - **nevirapine initiation in pregnancy (risk liver failure)**
- **All other ARV : insufficient data to recommend**

# *HIV-1+ pregnant woman presenting on therapy*

- Preconception care ++
- Adapt ARV if poor tolerance or poor viral load control
- Change as early as possible if efavirenz (French recommendations)
- If ARV with poor pregnancy data (raltegravir (Isentress), etravirine (Intelence), maraviroc (Celsentri), Rilpivirine (Edurant ou Eviplera)
  - Change if possible
  - Continue if necessary : resistance or poor tolerance with other options, drug interactions, pill burden issues, etc

# *HIV-1+ pregnant woman presenting without therapy late in pregnancy*

- Several different situations :
  - Woman knowing she is HIV+ but not taking ARV
  - 3d trimester screening
  - Screening in delivery room (TROD)

| Maternal therapy |
| --- |
| • 2 NRTI + 1 boosted PI<br>• Consider adding enfuvirtide SC or raltégravir |
| **Delivery** |
| • Planned cesarean section + IV zidovudine<br>• NVP single-dose if no pre-partum ARV |
| **Intensified neonatal prophylaxis** |
| • AZT+3TC+NVP |

# *Special cases*

| HIV-2 |
| --- |
| • **If HIV-2 RNA undetectable without ARV, CD4>500 : monotherapy in 3d trimester**<br>• **If HIV-2 RNA detectable and/or CD4<500 : triple 2 NRTI+ PI/r** |
| **HIV-1+ with spontaneously low HIV RNA** |
| • CD4 > 350 and VL < 4 Log without ARV<br>• **Consider simplified therapy (lopinavir/r monotherapy, PRIMEVA/ANRS 135, Tubiana et al. CID 2013)**<br>• **Intensify if VL > 400 c/ml at 8 wks** |
| **Co-infection with VHB** |
| • **tenofovir/FTC** |
| **Severe immune deficiency** |
| • **CD4<100 risk of opportunistic infections and immune restoration syndrome** |

# *Why do PMTCT failures occur ?*

- Poor viral load control due to :
  - Poor compliance
  - Late access to care
  - Obstetrical complications (preterm birth...)



ART, delivery ≥37 wks
(2001-2007)

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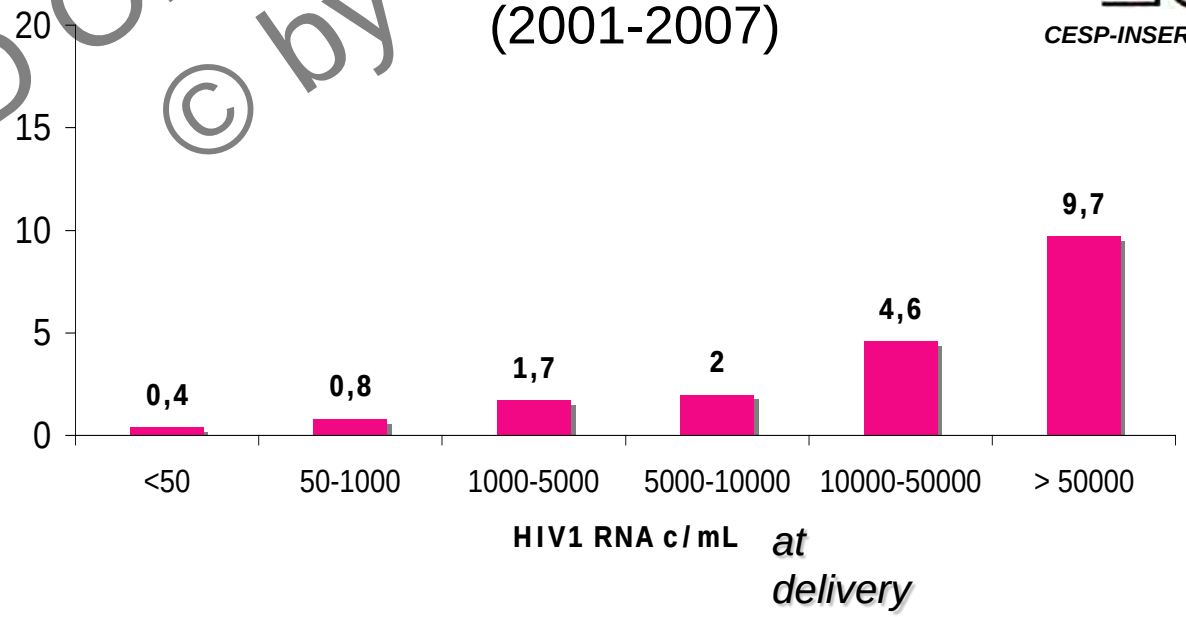
overall
MTCT
35/ 3729
= 0.94%



# *Exposure to HIV*

**In utero** **Intra-partum** **Breastfeeding**



**Exposure = risk but not necessarily transmission**

# *Prevention of MTCT*

**In utero** **Intra-partum** **Breastfeeding**

**ARV in pregnancy**
**Decrease viral load**

**ARV intra-partum pregnancy**
**Planned C-section**

**Neonatal ARV prophylaxis**

# *MTCT obstetrical risk factors*

- Mode of delivery : protective effect of planned CS
- Rupture of membranes
- Invasive procedures
  - > still relevant in women with undetectable VL on HAART ?

# MTCT of HIV-1 according to mode of delivery and maternal viral load

## women treated with ARV delivering ≥ 37 GW 2000-2010 , n=4634

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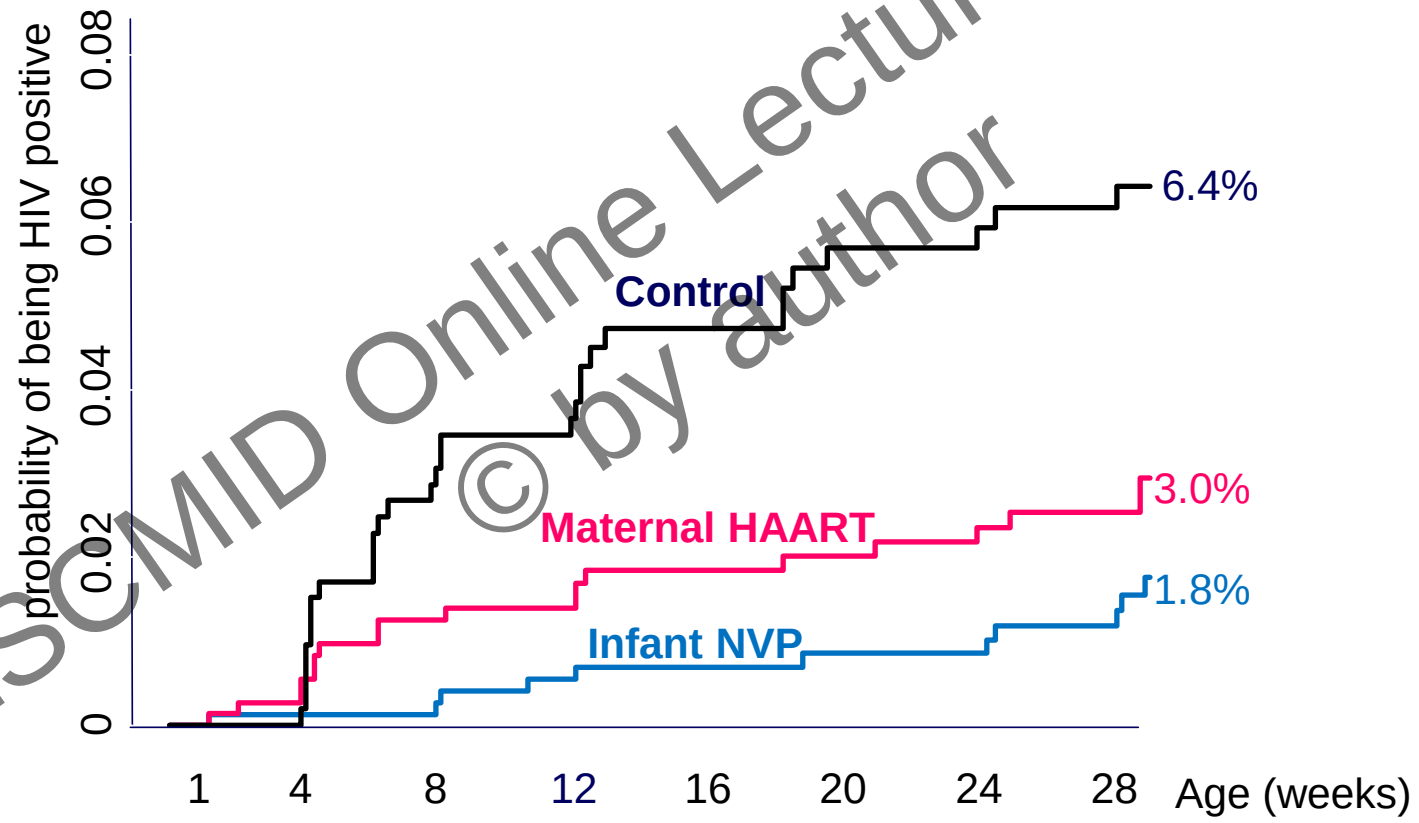
TABLE 1
**Mother-to-child HIV transmission in women receiving cART, 2000–2010**

| Variable | | (1) Vaginal delivery N | % | n | (2) Elective cesarean N | % | n | *P* value (1) vs (2) | (3) Nonelective cesarean N | % | n | *P* value (1) vs (3) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term deliveries (≥37 wk) | According to VL categories, copies/mL[a] | | | | | | | | | | | |
| | ≥10,000 | 25 | 4.0 | (1) | 113 | 5.3 | (6) | 1.00 | 31 | 9.7 | (3) | .41 |
| | 1000-10,000 | 52 | 1.9 | (1) | 160 | 0.6 | (1) | .43 | 49 | 0.0 | (0) | 1.00 |
| | 400-1000 | 37 | 0.0 | (0) | 100 | 0.0 | (0) | NA | 31 | 0.0 | (0) | NA |
| | 50-400 | 307 | 1.0 | (3) | 400 | 1.0 | (4) | 1.00 | 159 | 2.5 | (4) | .24 |
| | <50 | 1880 | 0.3 | (6) | 1195 | 0.3 | (3) | 1.00 | 703 | 0.3 | (2) | 1.00 |

*Briand et al AJOG 2103*

# *Breastfeeding and HIV*

# *Current breastfeeding options for HIV+ women in resource-poor settings*




**BAN study. Chasela et al. NEJM 2010**

# Conclusion

- Preconception counseling and testing : therapy and reproductive options
- The best prevention of MTCT is antiretroviral drugs during pregnancy
- PMTCT is a model for HIV prevention : TasP, PrEP
- More drugs, longer period -> maximum efficacy
- Toxicity issues : paradox use older drugs with safety data and toxicities vs. recent drugs without data
- Need for further follow-up and research

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