The combination of Tenofovir-Emtricitabine (Truvada®): a new antiretroviral (ARV) regimen for the prevention of mother-to-child transmission of HIV-1 (PMTCT) in resource-limited settings

Phase II clinical trial "TEmAA"

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(Principal Investigator)

Background
A limited number of ARVs and drug regimens for PMTCT

	Biodisponibility	Half-life	Placenta	Elimination
Zidovudine	63%	1 h	85%	Kidney
Lamivudine	86%	2-6 h	100%	Kidney
Nevirapine	90%	40 h	90%	Kidney

- Single-dose nevirapine (sdNVP) is the most common ARV regimen used for PMTCT: one 200 mg tablet at the onset of labor, together with one neonatal dose of syrup on Day 2 (HIVNET012 trial, Uganda)
  - Reduction of 47% of the rate of transmission in comparison with a a single-dose of zidovudine
  - Absolute rate of transmission at week 6 (breastfeeding) = 11.9%

Viral resistance: the most worrisome problem with the single-dose nevirapine regimen

- High rate of occurrence of NVP resistance mutations in the four weeks after exposure
  - in HIV-infected women (25-50%)
  - in HIV-infected children (20-87%)

Eshelman AIDS, 2001, Chaix CROI 2004, Arrive IJE, 2007

- Resistance acquired to all non nucleoside reverse transcriptase inhibitors (NNRTIs)

Is there an alternative to the single-dose nevirapine PMTCT regimen?

Tenofovir **Em**tricitabine in **A**frica and **A**sia

The ANRS 12109 - EDCTP TEmAA trial

Truvada®

- Truvada® is the combination of two antiretroviral drugs:
  - Tenofovir disporoxyl fumarate [TDF, 300 mg], nucleotidic analogue
  - Emtricitabine [FTC 200 mg], similar to 3TC
  - Elimination half-life: 12-18 h for TDF and 10 h for FTC
- Posology: 1 tablet of Truvada® per day in adults
- Animal studies with Tenofovir
  - Short-course is highly effective in protecting newborn macaques against SIV infection (Van Rompay JAIDS 2006)
  - No major toxicity in animal with high doses of TDF

Objectives of the ANRS 12109 - EDCTP TEmAA trial

- **Primary objective:**

  To study the pharmacokinetic properties of TDF and FTC in pregnant women and their newborns

- **Secondary objectives:**
  - To determine the safety and toxicity of TDF and FTC in pregnant women and their newborns
  - To estimate the frequency of TDF and FTC resistance mutations at 4 weeks postpartum in women and at 4 weeks of life in HIV-infected children
  - To determine the frequency of peripartum mother-to-child transmission of HIV-1 after the use of this ARV drug regimen

Method (1): Study design

- Phase II clinical trial: multicenter
  - Abidjan, Côte d'Ivoire (supported by EDCTP)
  - Soweto, South Africa
  - Phnom Penh, Cambodia

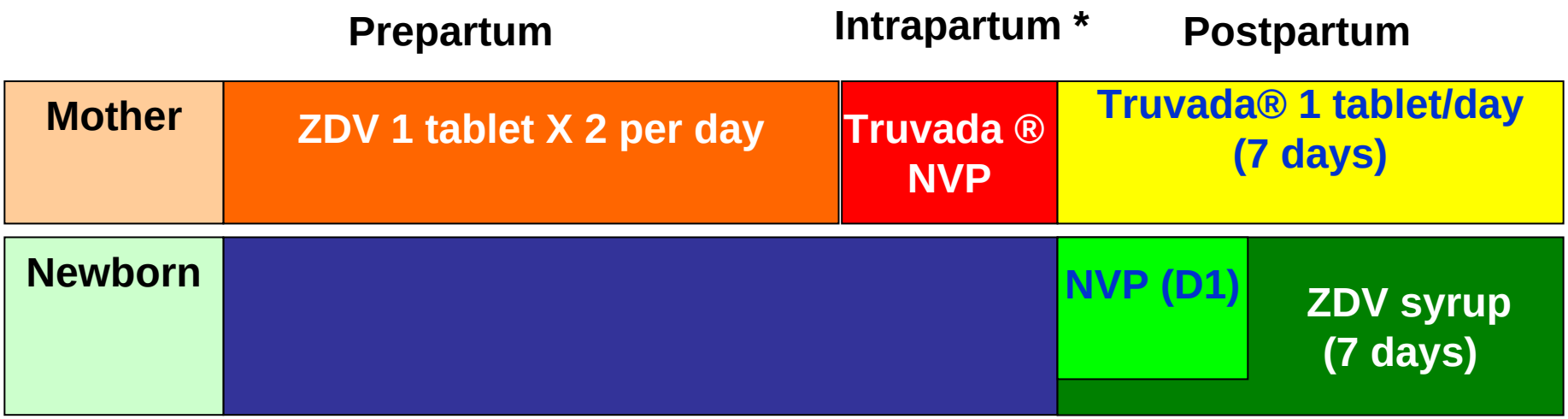
ANRS (France) Sponsor

- Two steps
  - First step: Initiation of Truvada ® in HIV-infected mothers only
  - Second step: Initiation of Truvada ® in HIV-infected mothers and syrup of TDF + FTC in their neonates

Method (2): Inclusion criteria

- Pregnant woman tested positive for HIV-1 or HIV-1 & 2
- Aged 18 years or older
- Haemoglobin ≥8 g/dL
- Creatinine clearance >49 mL/min
- Woman does not meet criteria for antiretroviral treatment for her own health during this pregnancy
  (CD4≥200/mm3 and stage 1 or 2 or CD4≥350/mm3 and stage 3)
- Must be antiretroviral-naïve
- Informed consent given by the mother and the father of the child to be born
- Mother consents to at least a three day hospital stay after giving birth

Method (3): First step Antiretroviral regimen



2 tablets of Truvada® (600 mg of TDF and 400 mg of FTC) and one tablet of NVP (200 mg)

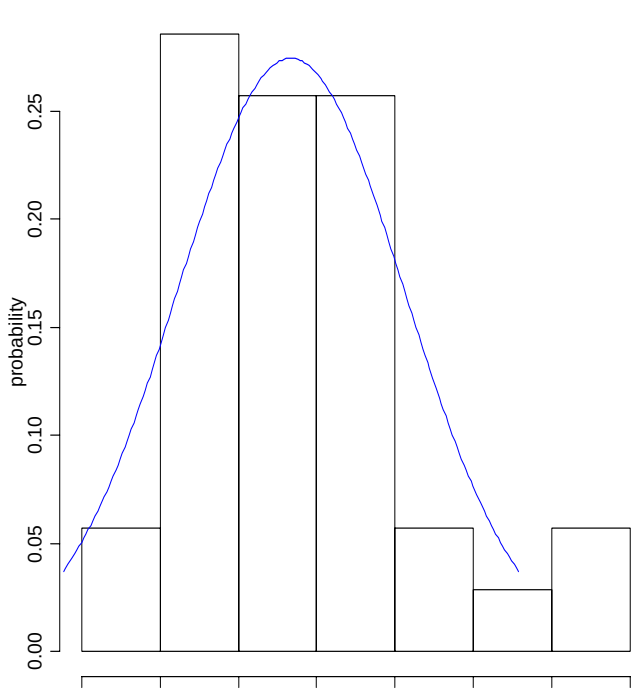
Method (4)
Timing of blood sample collection

	Mother	Neonate
Pharmacokinetics	H0, H1, H2, H3, H5, H8, H12, Delivery, H24, H48, D3, D7	Birth, D1, D2
Genotypic resistance	W4	W4
HIV transmission		D3, W4, W6

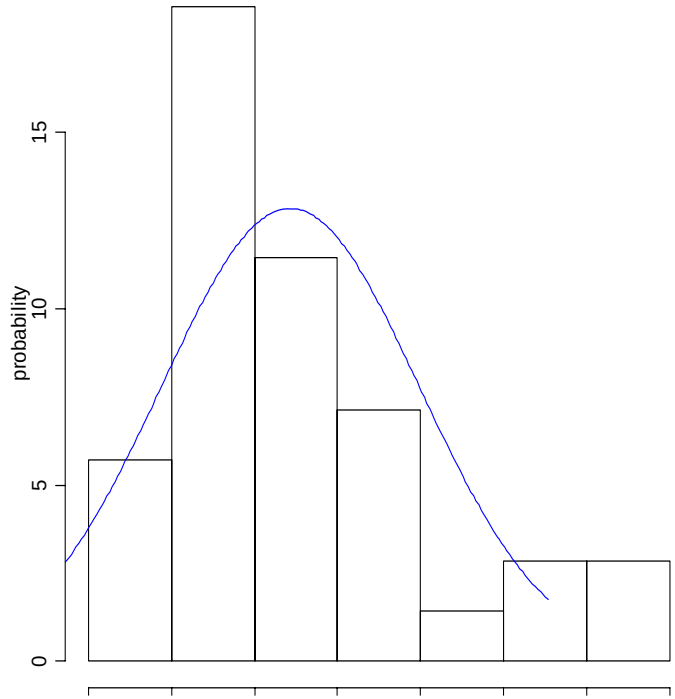
Result (1): Enrolment and baseline characteristics (N=19)

Variables	Median	Range
Age (years)	27	19 - 39
Gestational age	32	28 - 37
CD4 (cells/mm^3)	450	253-557
Viral load (log10)	4.1	3.8-5.2
WHO staging 1	10	(52%)
Hemoglobin (g/dL)	10.0	8.2-11.9

Results (1)
FTC maternal C_{min} and AUC



AUC

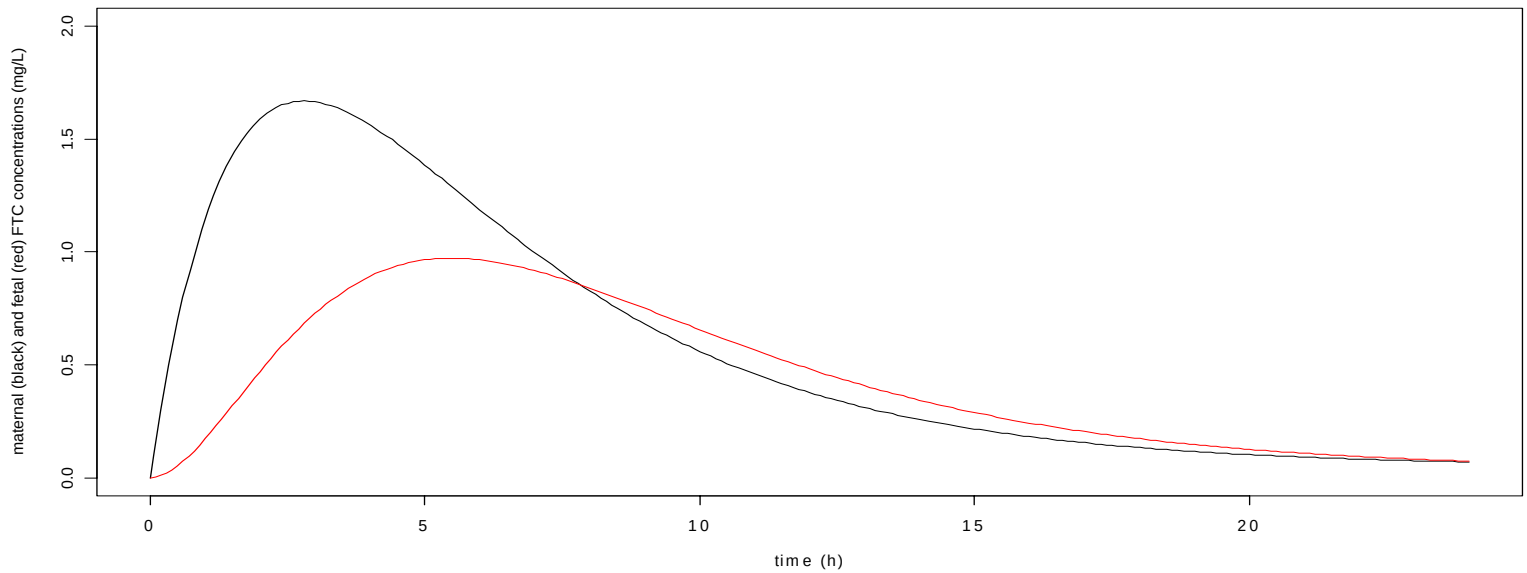


C_{min}

After the 400 mg FTC administration, in pregnant women
AUC = 15.5 mg.L-1.h, Tmax= 3.0 h,
Cmax 1.60 and Cmin = 0.14 mg/L

Results (2)
FTC: good placental transfer

- At delivery, median (range)
  - FTC maternal 1.02 (0.035–2.04) mg/L
  - Cord blood concentrations 0.74 (0.005–1.46) mg/L



Results (3) - Safety

- Mothers (n=19)
  - No clinical manifestations
  - Transient biological events (grade 3 or 4)
  - Anemia (n=1), hemorrhagia at delivery
    - Neutropenia and leucopenia (n=3)
    - Isolated neutropenia (n=2)
- Neonates (n=20)
  - Clinical serious adverse events (n=4)

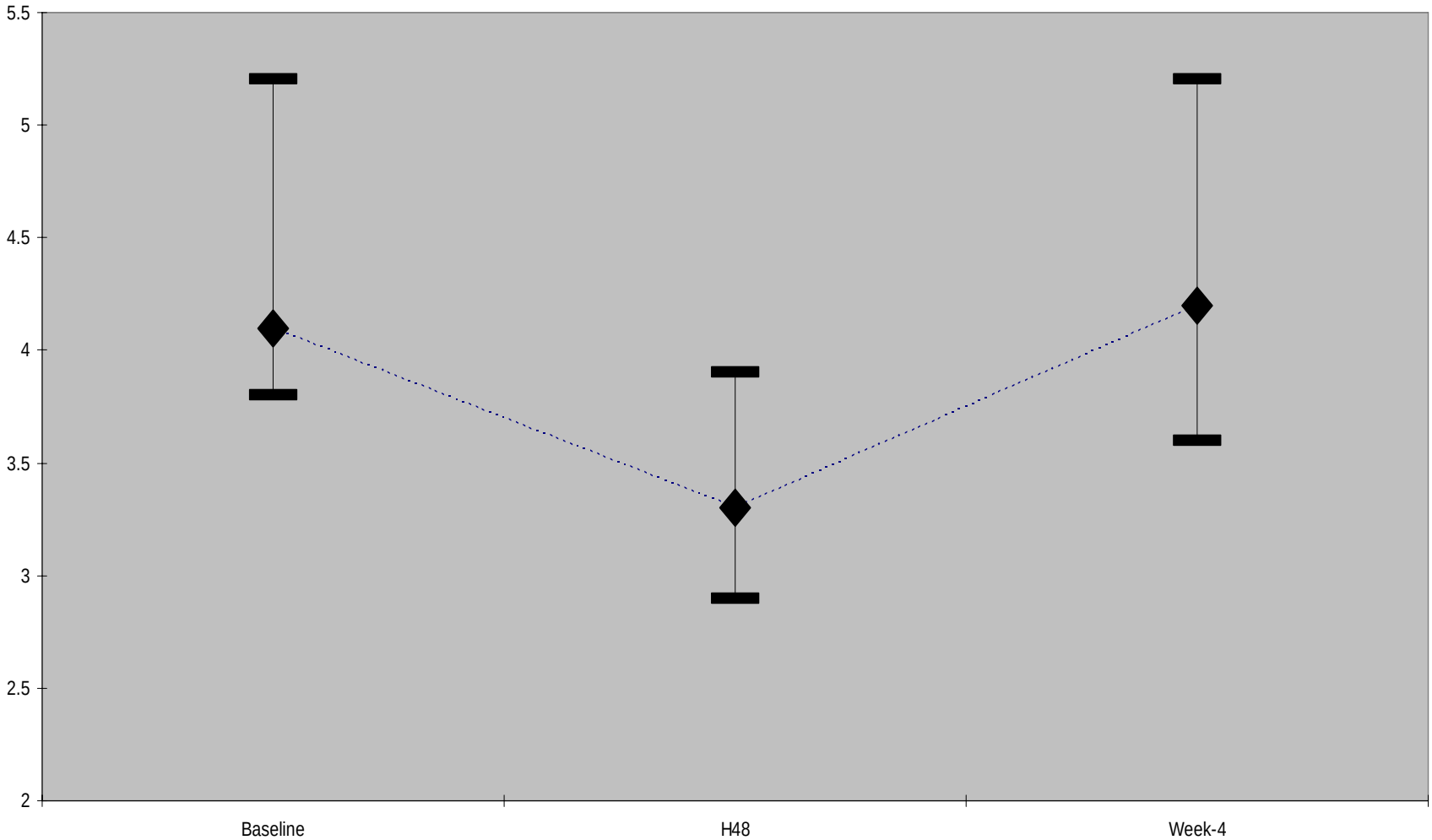
    3 deaths (1 twin with infectious gastroenteritis, 1 HIV-infected infant with intestinal occlusion and one with neurological symptoms at birth)
  - Transient biological events (grade 3): anemia (n=2)

Results (4)
Rate of HIV transmission

- One case of HIV transmission among 20 infants tested
  - One case of *in utero* infection
    - Day 2: PCR (3.80 log10, 6344 copies/ml)
    - Week 4: PCR (6.02 log10, 1050 000 copies/ml)
  - No case of intrapartum transmission

- This HIV-infected child died on day 26 before the initiation of ART and after seven days of hospitalization due to gastro intestinal symptomatology

Results (5) - Maternal kinetics of maternal plasma viral load over time



Results (6)
Viral resistance after exposure to ARVs for PMTCT

- Genotyping resistance test was available for 18 out of the 19 women at 4 weeks postpartum
- **No viral resistance** to ZDV, NVP, FTC or TDF were detected in the 18 virus tested (Upper limit of 95% CI: 17%).
- Phylogenetic analysis revealed the following strains:
  - CRF02-AG (n=14)
  - A (n=3)
  - CRF06 (n=1)

Lessons learned after step 1

- FTC was shown to have good placental transfer. Administering 2 mg/kg 12 hours after birth or a 1 mg/kg 6 hours after birth of FTC should produce neonatal concentrations comparable to those observed in adults

- TDF/FTC combination for PMTCT was well tolerated in women and exposed newborns with no intrapartum HIV transmission reported

- Providing 7 days of additional PP antiretroviral exposure with TDF/FTC immediately after sdNVP+TDF/FTC extended the suppression of viral replication, thus avoiding a PP exposure to NVP alone

Publications

Three abstracts submitted to the 2008 CROI conference

- Safety
  - Title : Tolerance After Short Course of Tenofovir Disoproxil Fumarate (TDF) and Emtricitabine (FTC) to Prevent Mother-to-Child Transmission (PMTCT) of HIV-1: the TEmAA ANRS 12109 Phase II Trial, Step 1 (Arrive E, et al)
- Virology
  - Absence of HIV-1 Resistance After Single-Dose Nevirapine (sdNVP) and Short Course of Tenofovir Disoproxil Fumarate (TDF) and Emtricitabine (FTC) to Prevent Mother-to-Child Transmission (PMTCT) of HIV-1: the TEmAA ANRS 12109 Phase II Trial, Step 1 (Chaix ML, et al)
- Pharmakokinetics
  - Population Pharmacokinetics of Emtracitabine (FTC) in HIV-1 infected Pregnant Women and their neonates (TEmAA - ANRS 12109) (Hirt D, et al)

Plan of action for the next step of the trial

- Data Safety Monitoring Board (DSMB) planned in December 2007
- Preparation of the step 2 of the trial: administration of TDF and FTC to neonates
  - New submission to national IRB of minor changes/amendments of the protocol if any (December 2007)
  - Start of enrolment (March 2008)
- Preparation of the phase III trial (design, site selection, …)

TEmAA scientific organization

- Sponsor: ANRS (Trial 12109) since September 2005
- Primary investigators:
  - Pr François Dabis (INSERM U593, ISPED, Bordeaux)
  - Dr Didier Ekouévi (PAC-CI/ACONDA, Abidjan - EDCTP Senior fellow)
- Co-investigators:
  - France: Prs Christine Rouzioux, Stéphane Blanche, Jean-Marc Treluyer
  - Côte d'Ivoire: Pr N'dri-Yoman
  - Cambodia : Pr Sim, Dr Eric Nerrienet,
  - South Africa : Prs Glenda Gray and James McIntyre
- Trial coordinator: Dr Elise Arrivé

Funding of TEmAA trial

- European & Developing Countries Clinical Trial Partnership (EDCTP):
  - Didier Ekouevi fellowship (March 2005 – February 2007)
  - For the Abidjan site and the overall trial data management center: 200 000 Euros
- Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS), Paris (France)
  - For Cambodia and South Africa sites
  - For Bordeaux coordination of the three sites
  - 500 000 Euros
- Gilead Sciences: provided the study drugs (Truvada tablets and syrups of Tenofovir and Emtricitabine)