

Tolerance and Viral Resistance after Single-dose Nevirapine (NVP) and Short-course of Tenofovir Disoproxil Fumarate and Emtricitabine (TDF/FTC) in Delivering Women and Neonates to Prevent Mother-to-child Transmission (PMTCT) of HIV-1: The TEMAA ANRS 12109

Elise Arrivé¹, Marie-Laure Chaix², Eric Nerrienet³, Stéphane Blanche⁴, Christine Rouzioux², Divine Avit⁵, Mandisa Nyati⁶, Sim Kruiy Leang⁷, Didier K. Ekouévi⁵, François Dabis¹ and the TEMAA ANRS 12109 Study Group

1,INSERM U897, ISPED, Université Victor Segalen, Bordeaux, France; 2 Laboratoire de virologie, Hôpital Necker Enfants Malades, Univ Paris-Descartes, Paris, France; 3 Laboratoire HIV/Hépatites, Institut Pasteur du Cambodge, Phnom Penh, Cambodia; 4 Service d'Immunologie et Hématologie Pédiatrique, Hôpital Necker Enfants Malades, Univ Paris-Descartes, Paris, France; 5 Programme PACC, ANRS Abidjan, Côte d'Ivoire; 6 Perinatal HIV Research Unit (PHRU), University of the Witwatersrand, Soweto, South Africa; 7 Service Gynécologie-Obstétrique de l'Hôpital Calmette, Phnom Penh, Cambodia



Abstract T-148

Elise.arrive@isped.u-bordeaux2.fr
Tel: +33 (0)5 57 57 48 10
Fax: +33 (0)5 57 57 56 30

Abstract

Background. Viral resistance occurs with high frequency after single-dose nevirapine (sdNVP) for PMTCT and alternative regimens are urgently needed. The safety and viral response of the TDF/FTC combination in HIV-1 infected pregnant women have been shown to be good (1). It is unknown whether this drug combination can be administered to neonates as well.

Methods. The TEMAA ANRS 12109 trial is an open label phase II trial conducted in Cambodia, Cote d'Ivoire, and South Africa. In this second part of the trial, all HIV-1-infected pregnant women received zidovudine (ZDV, 300 mg BID) from the day of enrollment, between the 28th and 38th weeks of gestation, until the beginning of labor, when sdNVP (200 mg) and 2 tablets of TDF/FTC were given. One daily tablet of TDF/FTC was then administered during 7 days postpartum (PP). All infants received sdNVP (2 mg/kg), sdTDF (13 mg/kg) (2) and sdFTC (2 mg/kg) (3) plus one week of ZDV (4mg/kg BID). Mothers and infants were followed for 2 months. Serious adverse events (SAEs), kinetic of maternal plasma HIV-1 RNA and neonatal HIV-1 plasma RNA at 3 and 28 days of life were assessed. Genotypic resistance testing and phylogenetic analysis of the reverse transcriptase sequences were performed at 4 weeks PP.

Results. 36 HIV-1 infected pregnant women were enrolled (15 in Abidjan, 9 in Phnom Penh and 12 in Soweto): median age 28 years, median CD4 count 462 cells/mm³ and median HIV-1 RNA 3.6 log₁₀ copies/mL. All women received sdTDF and sdFTC. Two infants had clinical SAEs (5%) including one who died (neonatal sepsis). One transient grade 3 neutropenia and 2 grade 3/4 hyperbilirubinemia were also reported. One (2.8%) HIV pediatric in utero infection was diagnosed. Genotypic viral resistance to NVP was detected in one mother out of 34 (2.9%) (11 CRF02-AG, 2 CRF06, 7 CRF01-AE, 2 B, 11 C and 1 indeterminate strains) but none to ZDV, FTC or TDF.

Conclusion. Giving the combination of TDF/FTC for PMTCT to women as well as to their neonates appears to be well tolerated and efficient in both populations.

References : (1) Arrivé et al. *AIDS* 2009; 23(7):825-833 (2) Hirt et al. *Clin Pharmacol Ther.* 2009;85(2):182-9 (3) Hirt et al. *AAC* 2009;53(3):1067-73

Background

- Despite the increasing access to antiretroviral (ARV) drugs in resource limited settings, single-dose nevirapine (sdNVP) +/- other ARV is still the main intervention to prevent mother-to-child transmission (Spensley 2009, Mandala 2009)
- NVP long half-life induces the selection of resistant viral strains that may impair the virological response to subsequent ARV treatment including a NNRTI in women and children (Lallemant 2004, Lockman 2007, Musiime 2009)
- The emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) combination is a potential alternative/complement to NVP (Chi 2007)

Objectives

- The objectives of this study were:
 - To study the pharmacokinetic properties of TDF and FTC in pregnant women and their newborns (in progress)
 - To evaluate the tolerance and the risk of peripartum mother-to-child transmission of HIV-1 and viral resistance after treatment interruption (this poster)
- In the first step of the study, the tolerance and viral response obtained with a TDF/FTC combination in HIV-1 infected pregnant women for PMTCT was shown to be good (Arrivé *AIDS* 2009)
- It is unknown whether this drug combination can be administered to neonates as well

Methods

- This multi-centered phase I/II clinical trial was conducted in two steps in Abidjan, Côte d'Ivoire, Soweto, South Africa and Phnom Penh, Cambodia; step 2 finished in July 2009

STEP 2	Prepartum from 28-38 weeks gestation	Start of the labour * 300 mg TDF/ 200 mg FTC	Postpartum 7 days
Women N=30	ZDV 300 mg BID	TDF/FTC* 2 tablets sdNVP	TDF/FTC* 1 tablet QD
Children N=30		sdNVP (D1)	ZDV syrup

- 2 additional tablets of TDF/FTC were given to the mother if labor > 12 hours

- 13 mg/kg sdTDF and 2 mg/kg sdFTC were administered to the newborns within 12 hours of life (Hirt *Clin Pharmacol Ther.* 2009; Hirt et al. *AAC* 2009)

- Follow-up: from enrolment (at 28-38 weeks of gestation for women, at birth for children) to 60 days after delivery
- Outcomes:
 - Number of serious adverse events (ANRS scale for adults and DAIDS scale for infants)
 - Kinetics of maternal plasma HIV-1 RNA viral load and HIV-1 infection status of infants at D28 of life (HIV RNA real time PCR)
 - Viral genotypic resistance to NVP, TDF and FTC at D28 postpartum, in women and infected infants

Results

Maternal baseline characteristics

Site	Abidjan n=15	Phnom Penh n=9	Soweto n=12	Total N=36
Median age (years)	30	27	28	28
Median gestational age (weeks)	35	29	32	33
WHO stage 1	11 (73%)	9 (100%)	11 (92%)	31 (86%)
Median CD4 count (cells/mL)	501	398	447	457

- All women received 2 tablets of TDF/FTC during labor, 6 hours in median (IQR: 4h45 - 7h20) before delivery
- All infants received single dose TDF/FTC, 2h15 in median after birth (IQR: 1h30 - 3h20)
- One mother/infant pair was lost to follow-up before the visit at 4 weeks after birth

Acknowledgments

We acknowledge the French Agence Nationale de Recherches contre le VIH/SIDA et les hépatites virales (ANRS) for sponsoring the trial, as well as the European and Developing Country Clinical Trials Partnership (EDCTP) and Sidaction for their additional financial support. We greatly thank the local investigators and their staff in the Formations Sanitaires Urbaines de Youpougon-Attie and Abobo-Avocatier, the Centre Hospitalier Universitaire de Youpougon and the Centre de Diagnostic et de Recherches sur le SIDA in Abidjan, in the Calmette Hospital and Pasteur Institute in Phnom Penh, and in the Perinatal HIV Research Unit, Lesedi Clinic in Soweto and BARC SA Clinical Trials in Johannesburg. We also thank the women who accepted to participate in the trial and their infants. We acknowledge Gilead Sciences for providing the study drugs.

Safety

Mothers: 2 biological SAEs (5%), all resolved:

- > one grade 3 leucopenia at the beginning of labour
- > one grade 4 neutropenia at Day-7 postpartum

Infants: 2 clinical SAEs (5%), including one death

- > severe respiratory distress and dehydration caused by probable infection with cutaneous origin
- > acute cerebral suffering at birth with probable obstetrical origin

3 biological SAEs at Day-28 after birth, resolved

- > one grade 3 neutropenia
- > two grade 3/4 hyperbilirubinemia

These events were unlikely to be related to TDF/FTC administration except for transient neutropenia

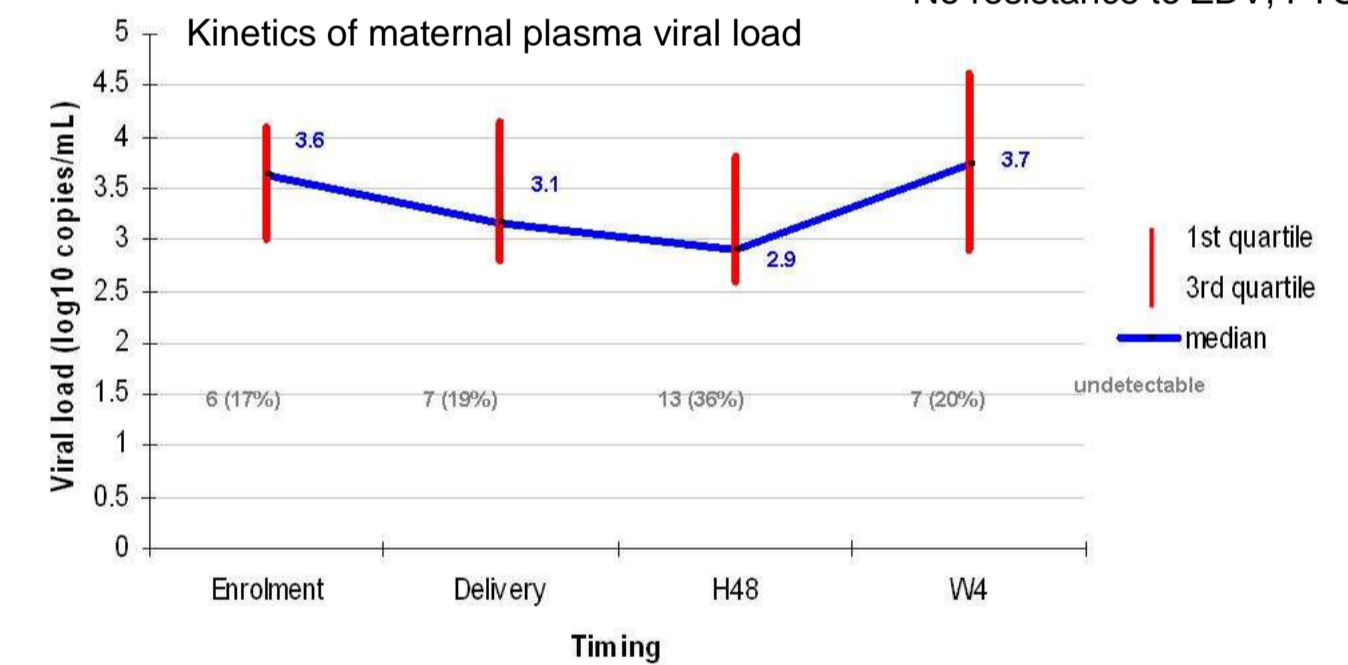
Virology

Viral phylogenetic analysis results for mothers

- Abidjan: CRF02-AG (n = 11), CRF06 (n = 2); 1 indeterminate, 1 in process
- Phnom Penh: CRF01-AE (n = 7), B (n=2)
- Soweto: C (n = 11); 1 lost-to-follow-up

-Viral resistance mutation (K103N) to NVP was detected in 1/33 mothers (95% CI: 0.0-15.8%) subtype C

-The mutation was present at enrolment and 48 hours after delivery in mixed viral population
-No resistance to ZDV, FTC or TDF was detected



Plasma HIV-1 RNA was detected in 1/36 infants at 3 days of life (in utero transmission) and in the same child out of 34 infants still followed-up at 28 and 45 days of life. The viral loads were 3.31; 4.93; 6.95 log₁₀ copies/mL at D3, D28 and D45, respectively. No resistance was detected at D3 or D28.

Conclusions

- TDF/FTC combination for PMTCT was well tolerated in women and in newborns.
- No intrapartum HIV transmission was reported.
- NVP resistance seemed to be avoided by providing 7 days of additional postpartum ARV exposure with TDF/FTC immediately after sdNVP+TDF/FTC.
- However, this regimen does not avoid the selection of pre-existing minority NVP resistant virus.