A European clinical pharmacology network to investigate the Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women

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Radboud University Nijmegen Medical Centre
The Netherlands

Investigator meeting at CROI 17-Feb-2010

1st PANNA Investigators Meeting: Paris, June 2008

2nd PANNA Investigators Meeting: Boston, Feb 2009

3rd PANNA Investigators Meeting: Venice, May 2009

4th PANNA Investigators Meeting: San Francisco, Feb 2010

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Agenda PANNA investigator meeting
17 February 2010

- Welcome
  David Burger 18:30 - 18:40

- General introduction and update Europe
  Angela Colbers 18:40 – 19:00

- Update Canada
  Charles la Porte 19:00 – 19:10

- Questions and closure
  David Burger 19:10 – 19:30

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Thanks to the sponsors of PANNA

- NEAT/PENTA
- Merck
- CTN (Canada)
- Negotiations with other companies are ongoing

Why study pharmacokinetics of ARVs in pregnant women?

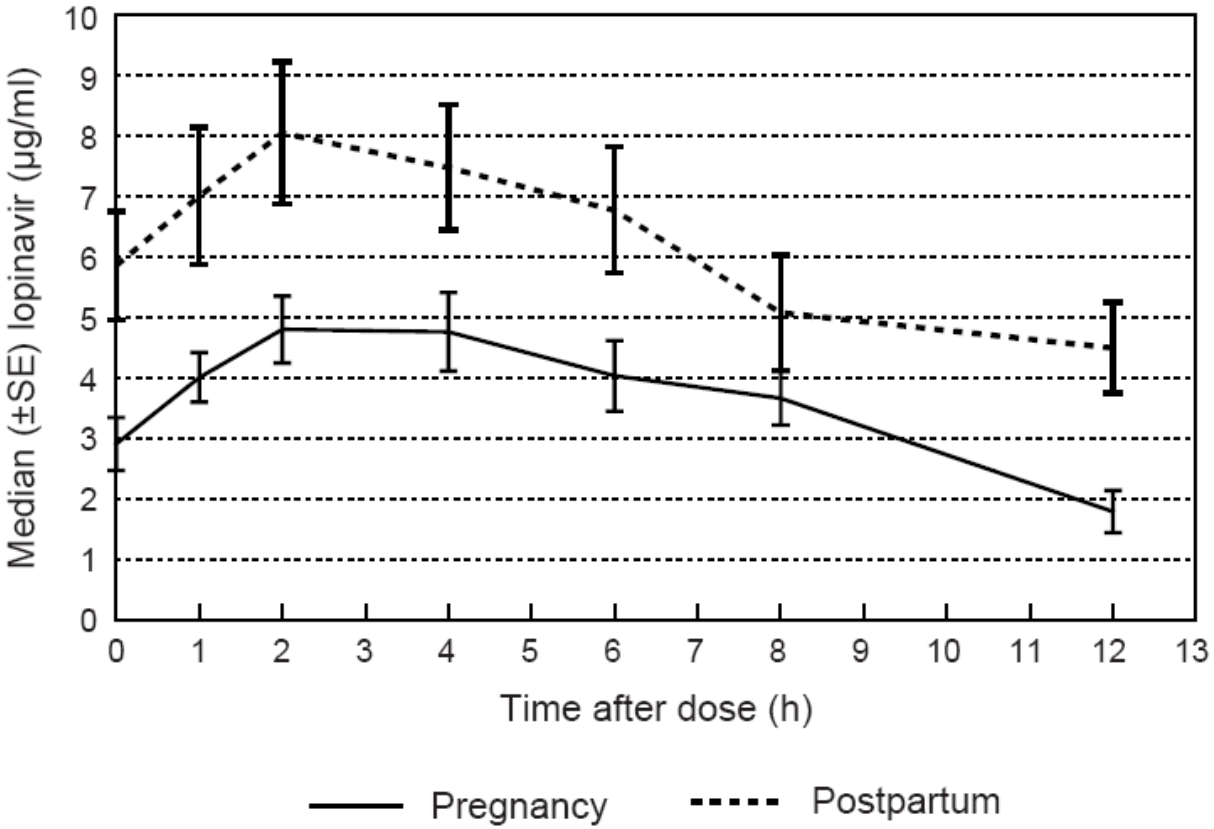
- Pregnancy may induce changes in PK of ARVs:
  - Increased volume of distribution
  - Reduced absorption from GI tract
  - Increased hepatic blood flow
  - Increased enzyme activity
  - Reduced protein binding
- In many cases *lower* plasma concentrations are the result
- Adequate exposure to ARVs is necessary to maximalize VL reduction
- Low VL is needed to prevent MTCT

Reduced lopinavir exposure during pregnancy

Alice M. Stek[a], Mark Mirochnick[b], Edmund Capparelli[c], Brookie M. Best[c], Chengcheng Hu[d], Sandra K. Burchett[e], Carol Elgie[f], Diane T. Holland[c], Elizabeth Smith[g], Ruth Tuomala[h], Amanda Cotter[i] and Jennifer S. Read[j] for the PACTG 1026s study team*

AUC: -28%

Cmin: -56%



AIDS 2006, **20**:1931–1939

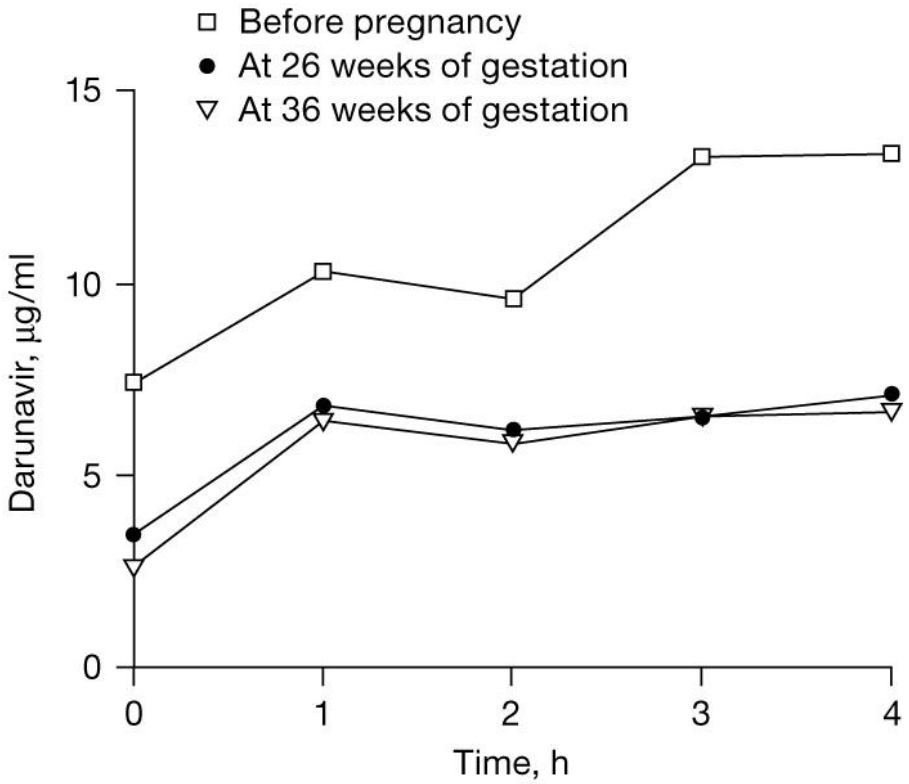
Antiviral Therapy 2010 15: in press (doi: 10.3851/IMP1473)

Case report

Decreased plasma levels of darunavir/ritonavir in a vertically infected pregnant woman carrying multiclass-resistant HIV type-1

Carmela Pinnetti[1], Enrica Tamburrini[1], Enzo Ragazzoni[2], Andrea De Luca[1], Pierluigi Navarra[2]*

AUC: -45%
Cmin: -61%



PANNA's mission:

Evidence-based dose recommendations for all ARVs to be used in pregnancy

Compounds under investigation

NNRTI

- Etravirine (class B) 200mg BID
- Efavirenz (class D) 600mg QD, UK/Ireland only

NRTI

- Emtricitabine (class B) 200mg QD
- Tenofovir (class B) 245mg QD

PI

- Atazanavir (class B) 300mg/100mg RTV QD; 400mg QD; 400/100mg QD
- Fosamprenavir (class C) 700mg/100mg RTV BID; 1400mg/200mg RTV QD
- Darunavir (class B) 600mg/100mg RTV BID; 800/100mg QD
- Tipranavir (class C) 500mg/200mg RTV BID
- Indinavir (class C) 800mg TID; 800mg/100mg RTV BID

Integrase inhibitor

- Raltegravir (class C) 400mg BID

Entry inhibitor

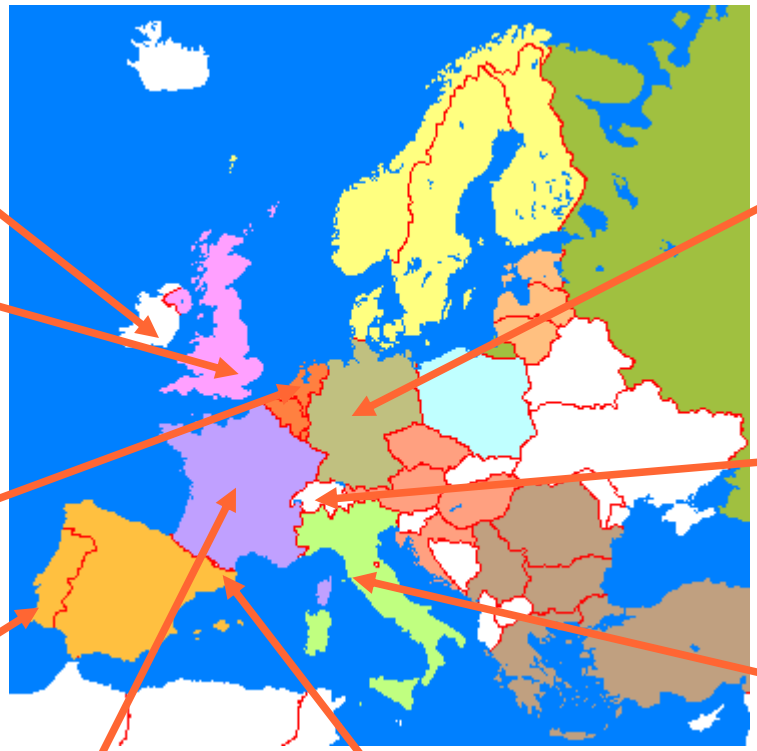
- Enfuvirtide (class B) 90mg BID
- Maraviroc (class B) 300mg BID

PANNA network collaboration

- Selection of sites capable of doing 12h or 24h PK recordings
  - Large site (preferably >40 deliveries/year)
  - Multidisciplinary team
  - Research unit/clinical ward & lab facilities (handling, storage)
  - Regional collaboration preferred
  - European (NEAT) & Canadian sites

- Target: sufficient sites to cover >500 deliveries/year

PANNA network



Canada

Dublin

London
3 centres

Nijmegen
Rotterdam
Amsterdam

Amadora

Paris

Barcelona

Roma
Torino
Padua

Geneva

Cologne
Bonn
Berlin
München
Frankfurt

Outline PANNA study protocol

- General study protocol, not specified per drug
  - Patient is eligible if HAART contains at least one drug from the list (no or limited PK information): efavirenz in UK and Ireland only
  - PK at third trimester (preferably Week 33) **and** >2 weeks PP (pref week 4-6)
  - N=16 per drug
  - Cord blood sampling at delivery
  - Safety/efficacy/adherence measurements
  - Central PK lab or local lab with sufficient QA/QC

Website: www.pannastudy.com

Status and milestones

- **6 patients included**
- 2 darunavir;
- 2 raltegravir;
- 3 atazanavir;
- 1 tenofovir

- The Netherlands, Spain, Italy open for inclusion
- UK: NA and ethics approval obtained. Local approval awaited.
- Germany: submitted for NA and EC approval
- Portugal, Ireland: NA and ethics being worked on
- Canada: funding approved
- December 2012:
    - For 5 drugs: data from 16 patients
    - Other agents: 5-10 patients

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http://www.pannastudy.com/main/inclusion

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PANNA study
Inclusion
Study centres
Participate as a new study centre

PANNA network

Inclusion of patients

The target population of the PANNA study are HIV-infected pregnant women who have an indication for treatment with a HAART regimen containing a newly developed antiretroviral agent for which there is insufficient data available on the pharmacokinetics during pregnancy. The selection of the antiretroviral agents is at the discretion of the treating physician.

Inclusion criteria

1. HIV-infected as documented by positive HIV
2. Subject is at least 18 years of age at screeni
3. Subject is willing and able to sign the Inform
4. Treated with an HAART regimen containing at agent has been taken for at least 2 weeks b
5. Subject is pregnant.
6. Subject is able to adhere to food intake reco

Exclusion criteria

1. Relevant history or current condition that mig excretion.
2. Inability to understand the nature and exten
3. Presence of grade III/IV anaemia (i.e. Hb <4

Test products

Test products

Below you will find an overview of the antiretroviral agents that we will investigate in the PANNA study. The number of patients still needed is mentioned in the last column. Please contact the study centre near you to include a patient treated with one of these agents.

Inclusion of patients

Drug name	Class	Dose and frequency	# pt included	# patients needed (16-#included)
Efavirenz, Stocrin®, EFV	NNRTI	600mg QD	0	16
Etravirine, Intelence®, TMC125	NNRTI	200mg BID	0	16
Emtricitabine, Emtriva® or FTC	NRTI	200mg QD	0	16
Tenofovir, Viread®, TDF	NtRTI	245mg QD	1	15
Atazanavir, Reyataz®	PI	300/100mg RTV QD 400mgQD 400/100mg RTV QD	3	13
Fosamprenavir, Telzir®, FPV	PI	700mg/100mg RTV BID 1400mg/200mg RTV QD	0	16
Darunavir, Prezista®, TMC114	PI	600mg/100mg RTV BID 800mg/100mg QD	2	14
Tipranavir, Aptivus®, TPV	PI	500mg/200mg RTV BID	0	16
Indinavir, Crixivan®	PI	800mg TID 800mg/100mg RTV BID	0	16
Raltegravir, Isentress®	integrase inhib	400mg BID	2	14
Enfuvirtide, Fuzeon®	entry inhibitor	90mg BID	0	16
Maraviroc, Celsentri®	entry inhibitor	300mg BID	0	16

Disclaimer Sitemap

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Contact details

- Project coordinator: Mrs Angela Colbers: A.Colbers@akf.umcn.nl

- Principal Investigator: Dr David Burger: D.Burger@akf.umcn.nl