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


Radboud University Nijmegen Medical Centre
The Netherlands

Investigator meeting in Glasgow 8-Nov-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

5th PANNA Investigators Meeting: Glasgow, Nov 2010

UMC St Radboud

# Agenda PANNA investigator meeting
# 8 November 2010

- Welcome & introduction of attendants
  David Burger 17:00 - 17:10
- General introduction and update including first results
  Angela Colbers 17:10 – 17:30
- Interactive part: problems to be solved
  Angela Colbers 17:30 – 18:00
- Questions and closure
  David Burger 18:00 – 18:10

panna

## Thanks to the sponsors of PANNA

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

# Why study pharmacokinetics of ARVs in pregnant women?

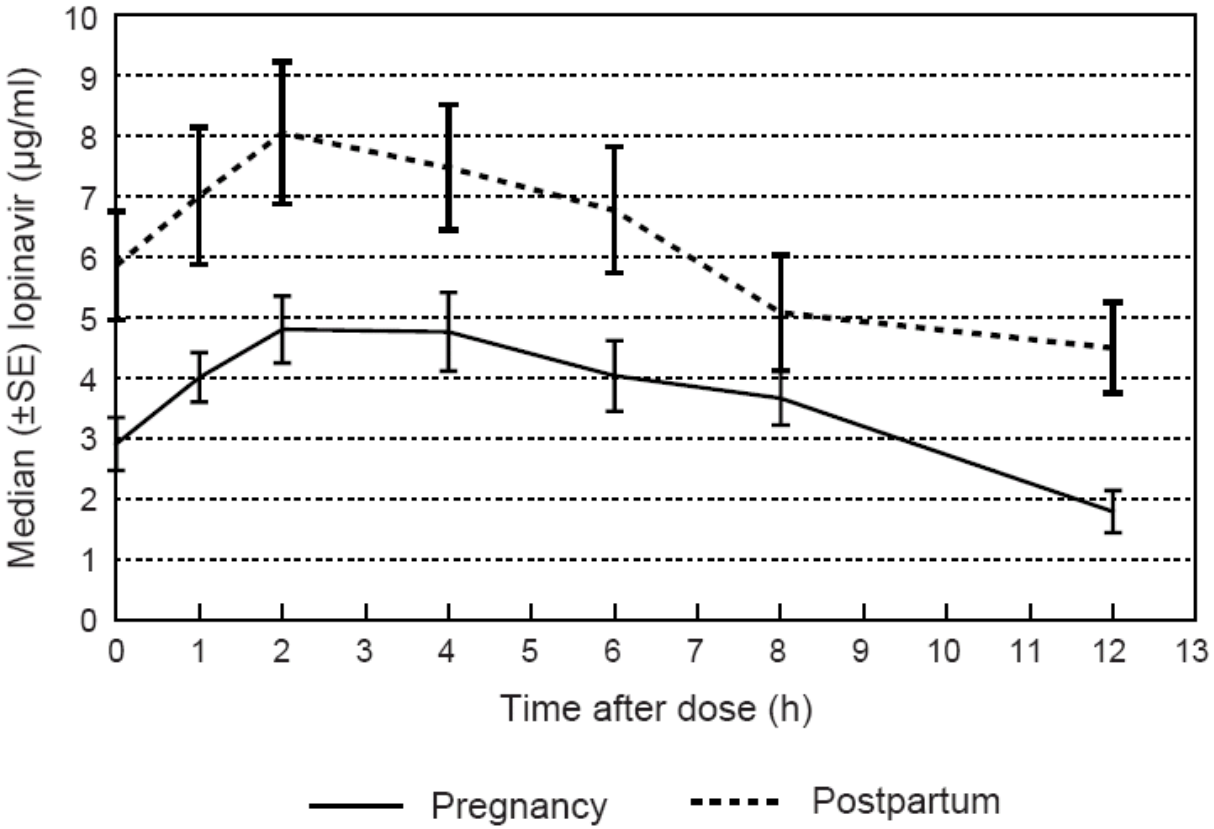
- Pregnancy may induce changes in PK of ARVs:
  - Increased volume of distribution
  - Reduced absorption from GI tract
  - Increased hepatic blood flow
  - Increased enzyme activity
  - Reduced protein binding
- In many cases *lower* plasma concentrations are the result
- Adequate exposure to ARVs is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

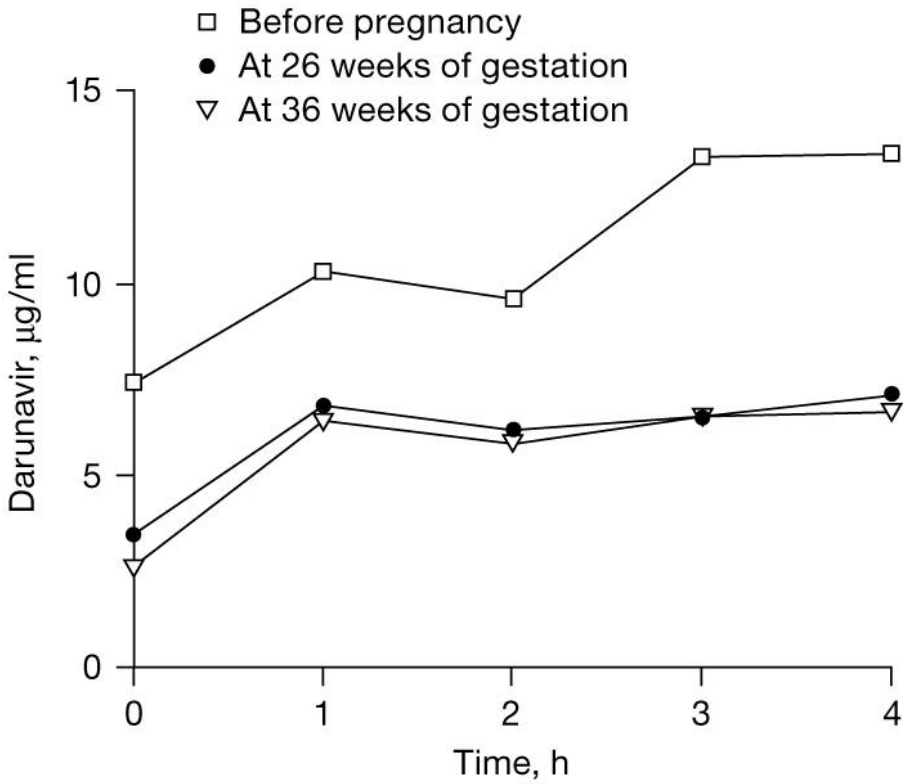
Antiviral Therapy 2010 15: in press (doi: 10.3851/IMP1473)

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**

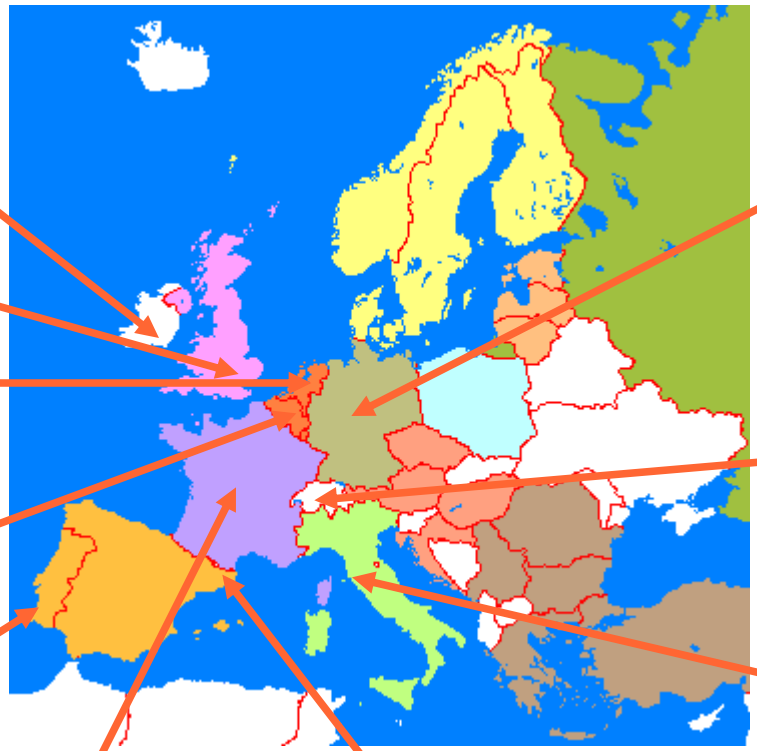
- Enfuvirtide (class B) 90mg BID
- Maraviroc (class B) 300mg BID

# 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

Brussels

Amadora

Paris

Barcelona

Roma
Torino
Padua

Geneva

Cologne
Bonn
Berlin
München
Frankfurt


North Pole
Norwegian Sea
Norway
Polar Ice
Greenland Sea
UK
Russia
Arctic Ocean
Ellesmere Island
Alert
Kalaallit Nunaat (Grønland) (Denmark)
Iceland
North Magnetic Pole
Bering Strait
Arctic Circle
Beaufort Sea
Banks I.
Resolute
Baffin Bay
Alaska (USA)
Inuvik
Victoria Island
Baffin Island
Davis Strait
Dawson
Great Bear Lake
Gjoa Haven
Yukon Territory
Whitehorse
Northwest Territories
Nunavut
Iqaluit
Labrador Sea
Atlantic Ocean
Yellowknife
Baker Lake
Great Slave Lake
Fort Nelson
CANADA
Ungava Bay
Newfoundland and Labrador
Nain
British Columbia
Prince George
Fort McMurray
Alberta
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Saskatchewan
Saskatoon
Regina
Churchill
Manitoba
Winnipeg
Hudson Bay
Kuujjuaq
Churchill Falls
St John's
Pacific
Ocean
Sandy Lake
James Bay
La Grande Rivière
Sept-Îles
Quebec
Saint-Pierre et Miquelon (France)
Prince Edward Island
Charlottetown
New Brunswick
Nova Scotia
Halifax
Fredericton
Thunder Bay
Ontario
United States of America
Lake Superior
Lake Michigan
Lake Huron
Lake Erie
Lake Ontario
Atlantic Ocean
LEGEND
National capital
Provincial or Territorial capital
Other populated places
International boundary
Provincial or Territorial boundary
Exclusive 200 nautical mile Economic Zone (EEZ)
© 2001. Her Majesty the Queen in Right of Canada, Natural Resources Canada.
Scale
300 0 300 600 900
km km

# 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

is at the discretion of the treating physician.

## Inclusion criteria

1. HIV-infected as documented by positive HIV antibody test and confirmed by an antigen test.
2. Subject is at least 18 years of age at screening.
3. Subject is willing and able to sign the Informed Consent Form prior to screening evaluations.
4. Treated with an HAART regimen containing at least one agent which is mentioned in Appendix 1; this agent has been taken for at least 2 weeks before the day of first PK curve evaluation.
5. Subject is pregnant.
6. Subject is able to adhere to food intake recommendations.

## Exclusion criteria

1. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.
2. Inability to understand the nature and extent of the study and the procedures required.
3. Presence of grade III/IV anaemia (i.e. Hb <4.6 mmol/L or <7.4 g/dL).

## 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 | 1 | 15 |
| Emtricitabine, Emtriva® or FTC | NRTI | 200mg QD | 5 | 11 |
| Tenofovir, Viread®, TDF | NtRTI | 245mg QD | 5 | 11 |
| Atazanavir, Reyataz® | PI | 300/100mg RTV QD<br>400mgQD<br>400/100mg RTV QD | 3 | 13 |
| Fosamprenavir, Telzir®, FPV | PI | 700mg/100mg RTV BID<br>1400mg/200mg RTV QD | 0 | 16 |
| Darunavir, Prezista®, TMC114 | PI | 600mg/100mg RTV BID<br>800mg/100mg QD | 5 | 11 |
| Tipranavir, Aptivus®, TPV | PI | 500mg/200mg RTV BID | 0 | 16 |
| Indinavir, Crixivan® | PI | 800mg TID<br>800mg/100mg RTV BID | 0 | 16 |
| Raltegravir, Isentress® | integrase inhib | 400mg BID | 5 | 11 |
| Enfuvirtide, Fuzeon® | entry inhibitor | 90mg BID | 0 | 16 |
| Maraviroc, Celsentri® | entry inhibitor | 300mg BID | 0 | 16 |

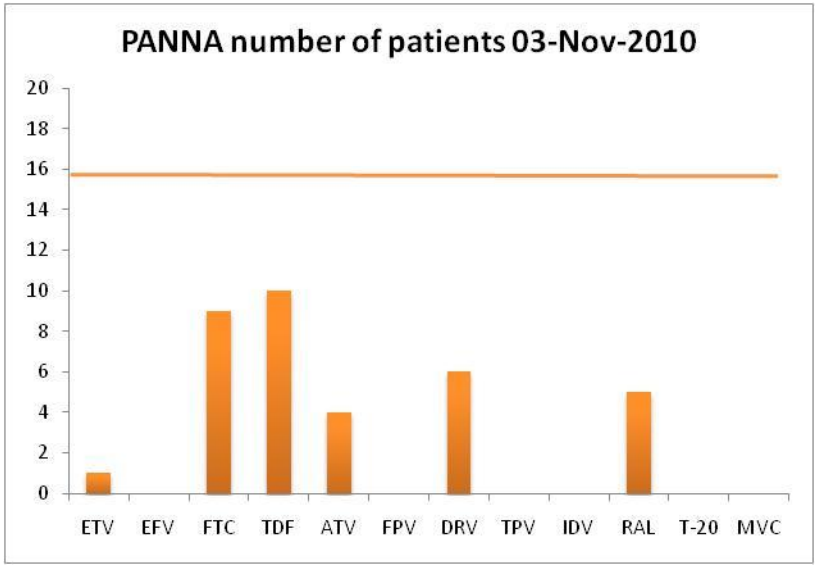
# Status and milestones

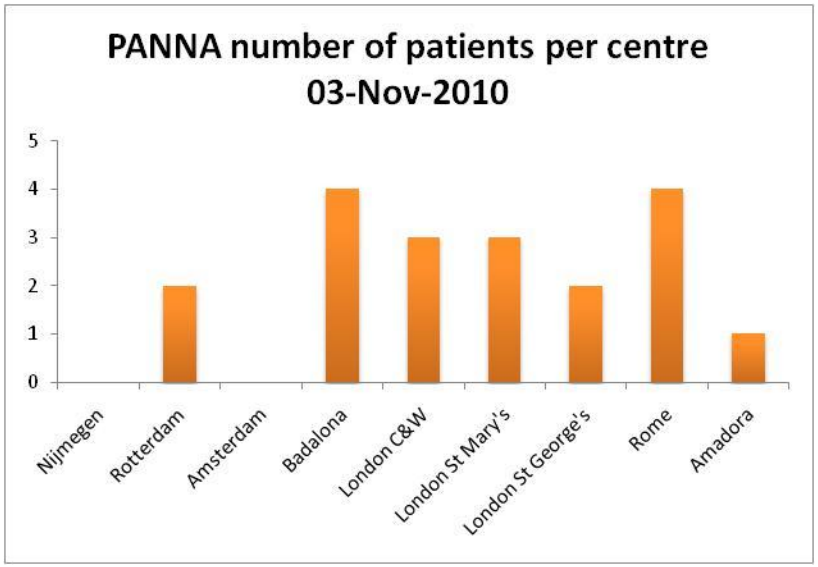
- The Netherlands, Spain, Italy, UK, Germany, Ireland (?), Canada (Ottawa) open for inclusion
- Portugal, Belgium, France: NA and ethics being worked on

- December 2012 TARGET:
  - For 5 drugs: data from 16 patients
  - Other agents: 5-10 patients

- November 2010:
  - Included 19 patients; 4 dropped out prior to first curve; 2 did not have a post partum curve
  - 6 compounds

# Status and milestones



# Preliminary results

Presented at the meeting, confidential data, not for the public (yet)

# Problems to be discussed

- Patients who take the medication once daily and at night

Change this to morning intake for one week (starting one week before the curve day):

Monday evening

Tuesday-Sunday  morning

Monday CURVE day morning

Tuesday morning AND evening

Wednesday evening etc.

- Other solutions: evening/night curve? Start 15:00 h and skip 12h sample?

- Meals

Preferably the meal mentioned on the CRF; however: most important is that the patient takes the same breakfast each PK day

# Problems to be discussed

- Logistics regarding cord blood sampling

Examples of how to arrange it. Different for each site.

- Reporting serious adverse events

If a patient has been admitted to the hospital due to complications: this should be reported as SAE.

- Reporting adverse events

All adverse events must be reported.

- Atazanavir amendment

Extra blood sample (trough) for patients on ATV/r 300/100 mg QD at 12 weeks post partum. This has been added on request of BMS. Amendment (+ adapted subejct information) accepted in UK, Germany, The Netherlands, Spain. Italy?

# Problems to be discussed

- Convince the patient to have the post partum curve taken

Tips from the centres?

# Contact details


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

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