

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

**panna**

Radboud University Nijmegen Medical Centre  
The Netherlands

PENTA INVESTIGATORS' MEETING 6 MAY 2011

# panna

- Why?
- What?
- How?
- Where?
- Status update / first preliminary results
- Questions

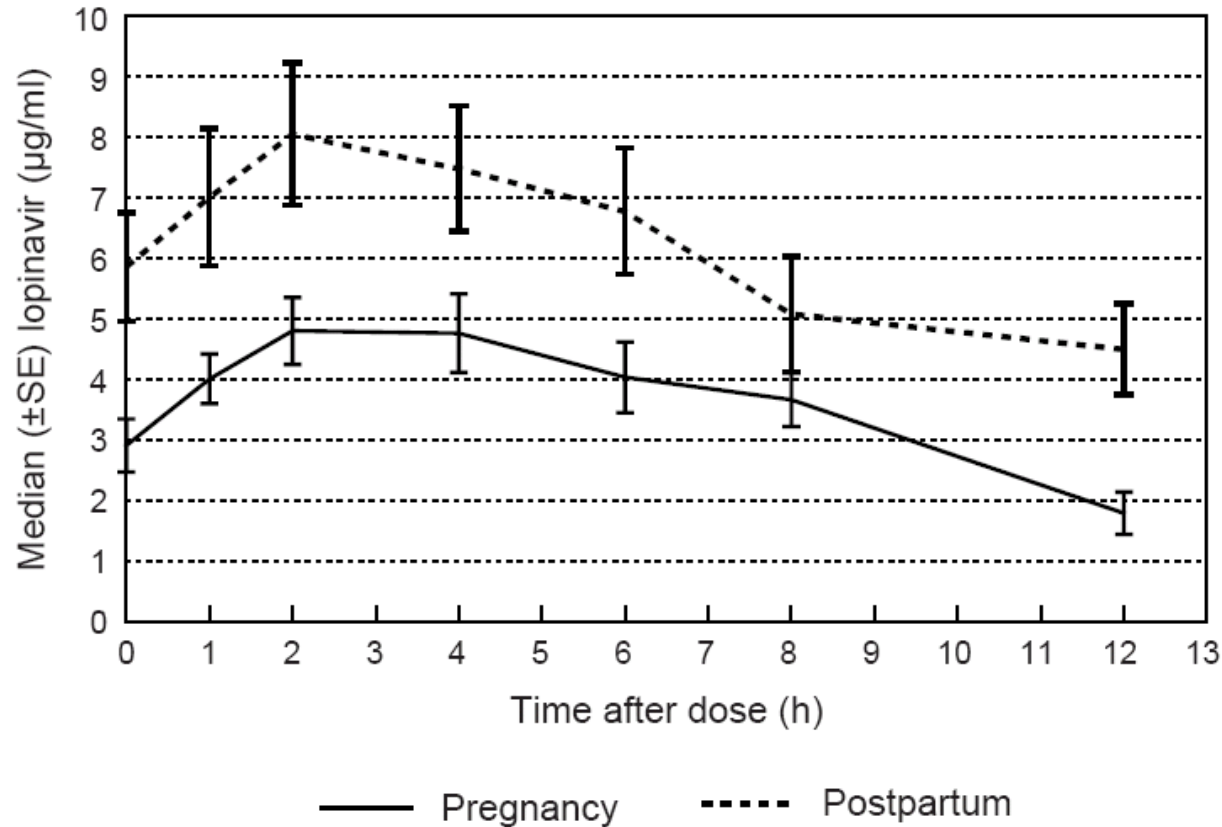
# Why study pharmacokinetics of ARVs in pregnant women?

- 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 maximalise VL reduction and prevent resistance
- Low VL is needed to prevent MTCT

## Reduced lopinavir exposure during pregnancy

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 Brookie M. Best<sup>c</sup>, Chengcheng Hu<sup>d</sup>, Sandra K. Burchett<sup>e</sup>,  
 Carol Elgie<sup>f</sup>, Diane T. Holland<sup>c</sup>, Elizabeth Smith<sup>g</sup>,  
 Ruth Tuomala<sup>h</sup>, Amanda Cotter<sup>i</sup> and Jennifer S. Read<sup>j</sup>  
 for the PACTG 1026s study team\*

AUC: -28%  
 Cmin: -56%

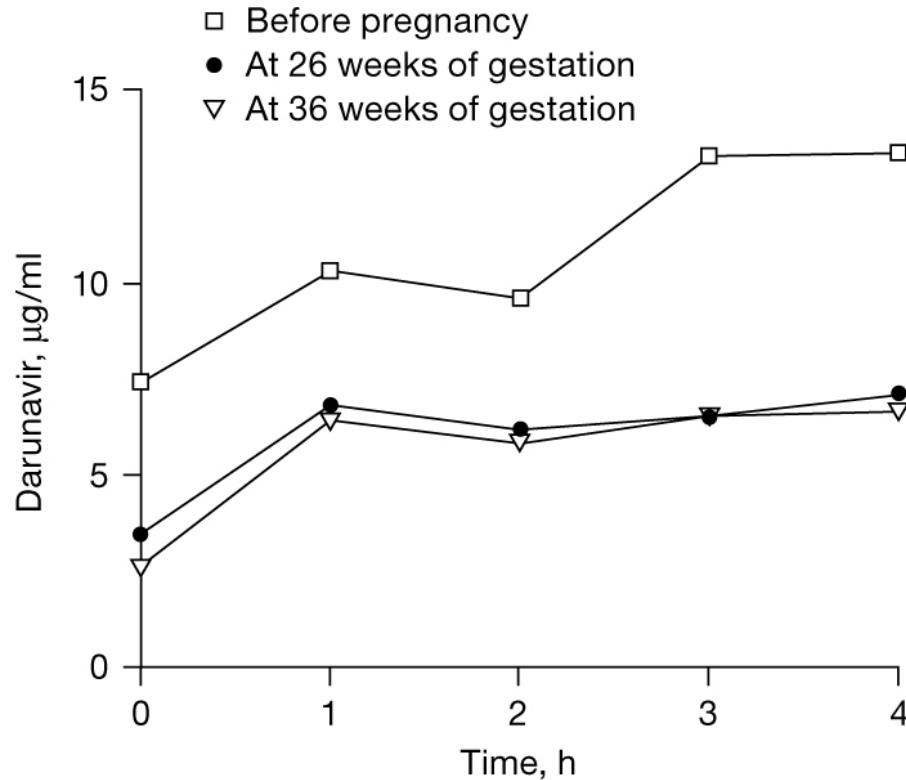


*AIDS* 2006, **20**:1931–1939

## Case report

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

*Carmela Pinnetti<sup>1\*</sup>, Enrica Tamburrini<sup>1</sup>, Enzo Ragazzoni<sup>2</sup>, Andrea De Luca<sup>1</sup>, Pierluigi Navarra<sup>2</sup>*



AUC: -45%  
 Cmin: -61%

# Pharmacokinetics in US Guidelines

| Antiretroviral Drug              | Pharmacokinetics in Pregnancy  | Concerns in Pregnancy  | Recommendations for Use in Pregnancy   |
|----------------------------------|--|--|--|
| <b><u>Recommended Agents</u></b> |  |  |  |
| Lopinavir/ritonavir              | Pharmacokinetic studies of the new lopinavir/ritonavir tablet formulation are under way, but data are not yet available. | No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) [2]. Well-tolerated, short-term safety demonstrated in Phase I/II studies. | Pharmacokinetic studies of the new tablet formulation are under way but are not yet conclusive as to the optimal dose in pregnancy. Some experts would administer standard dosing (2 tablets twice daily) throughout pregnancy and monitor virologic response and lopinavir drug levels, if available. Other experts, extrapolating from the capsule formulation pharmacokinetic data, would increase the dose of the tablet formulation during the third trimester (from 2 tablets to 3 tablets twice daily), returning to standard dosing postpartum. <del>Once-daily lopinavir/ritonavir dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.</del> |

***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 C) 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

# 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
  - Sparse PK sampling of the child if treated with the compounds on the list
  - Safety/efficacy/adherence measurements
  - Central PK lab or local lab with sufficient QA/QC

# Outline PANNA study protocol

## Delivery

- Date of delivery
- Way of delivery
- Weight mother

## Information on the child:

- Gender
- Body weight at birth
- DNA PCR child
- Congenital abnormalities reported?
- APRegistry form will be attached

# Outline PANNA study protocol

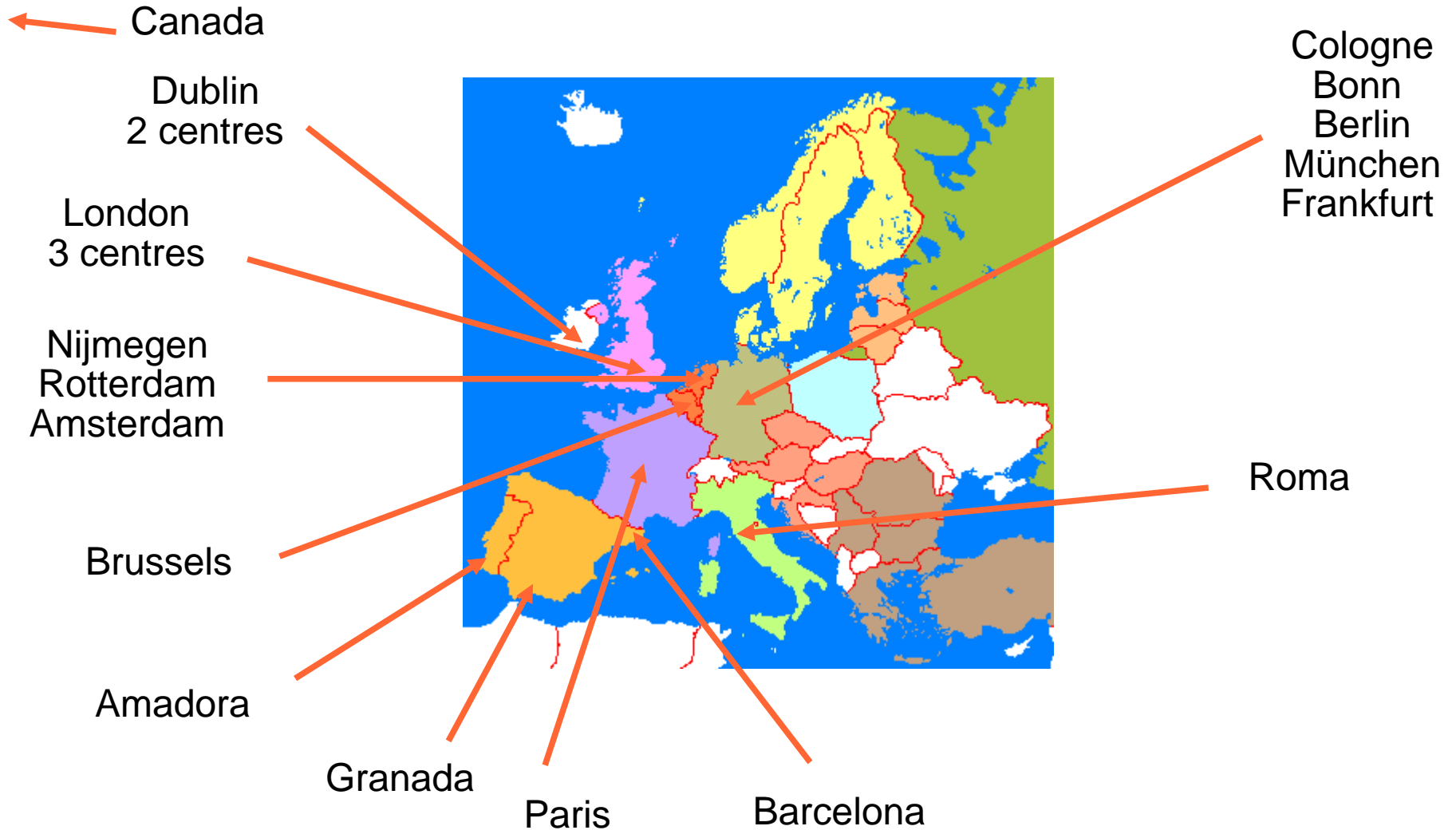
PK part only in case the child needs treatment with one of the listed compounds

| Item                   | Week1 | Week 3 | Week 4 or 6 |
|------------------------|-------|--------|-------------|
| Demographics           | X     |        |             |
| Body weight            | X     | X      | X           |
| Drug levels            | X     | X      | X           |
| Adverse events         | X     | X      | X           |
| Concomitant medication | X     | X      | X           |

## 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





# Website: [www.pannastudy.com](http://www.pannastudy.com)

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**PANNA**

PANNA is the name of the study of Pharmacokinetics of newly developed ANTiretroviral agents in HIV-infected pregNAnt women (PANNA). The purpose of the study is to collect pharmacokinetic data (PK curves) in pregnant HIV-infected women using newly developed antiretroviral agents.

**Setting up a European-Canadian network**

The group of pharmacist David Burger (Radboud University Nijmegen Medical Centre, The Netherlands) has set up a European-Canadian network of centres that are willing and able to participate in this study.

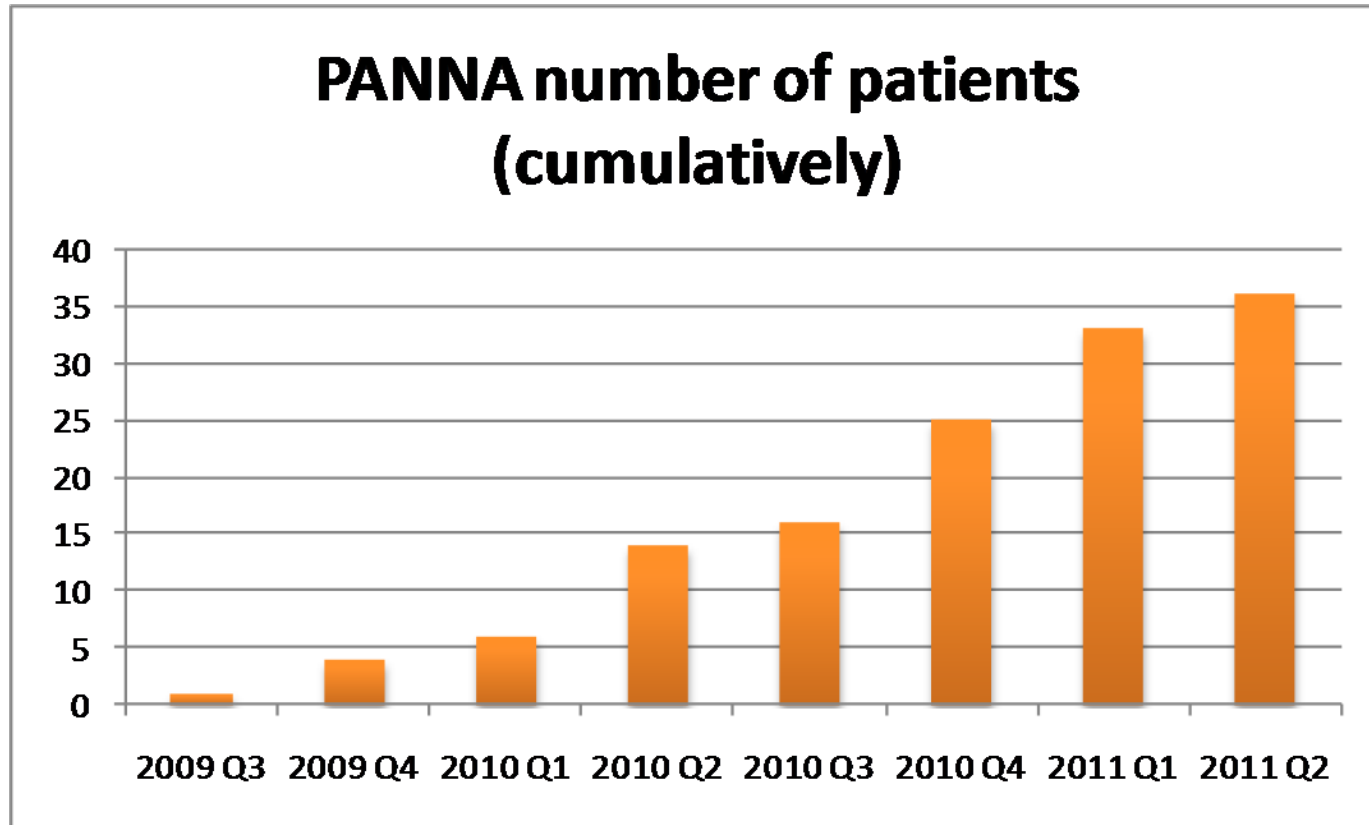
This website gives information about the study, how physicians can include patients and how centres can participate in the PANNA study.

PANNA study  
Inclusion  
Study centres  
Participate as a new study centre  
PANNA network

## Status and milestones

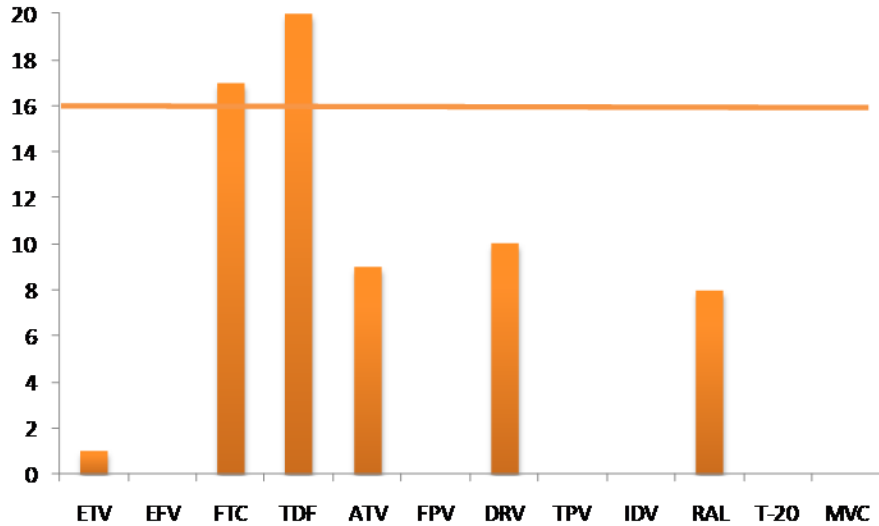
- First exploratory meeting during PENTA meeting June 2008
- May 2011:
  - 17 Centres open for inclusion: The Netherlands (3), Spain (2), Italy (1), UK (3), Germany (5), Ireland (2), Belgium (1)
  - Ottawa, Portugal, France: NA and ethics being worked on
  - 36 patients included; 4 dropped out prior to first curve; 2 did not have a post partum curve
  - 6 compounds
- December 2012 TARGET:
  - For 5 drugs: data from 16 patients
  - Other agents: 5-10 patients

## Status and milestones

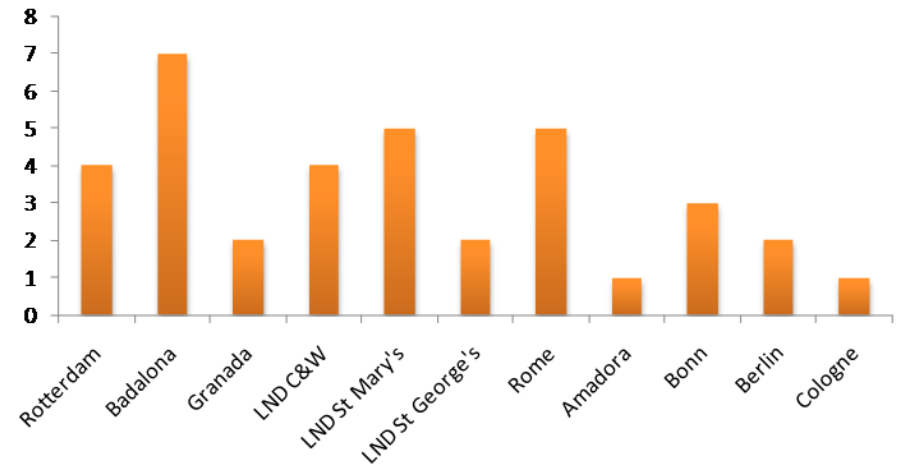


# Status and milestones

**PANNA number of patients 03-May-2011**



**PANNA number of patients per centre 03-May-2011**



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Home Contact

## 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 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, 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

## 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   | 17            | 0                                |
| Tenofovir, Viread®, TDF        | NRTI            | 245mg QD   | 20            | 0                                |
| Atazanavir, Reyataz®           | PI              | 300/100mg RTV QD<br>400mg QD<br>400/100mg RTV QD | 9             | 7                                |
| 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            | 10            | 6                                |
| 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  | 8             | 8                                |
| Enfuvirtide, Fuzeon®           | entry inhibitor | 90mg BID   | 0             | 16                               |
| Maraviroc, Celsentri®          | entry inhibitor | 300mg BID  | 0             | 16                               |

# First preliminary results raltegravir Presented as poster at HIV PK workshop April 2011

## Subject characteristics

| 3rd trimester (n=6)                                      |            |   |
|--|------------|---|
| age (years)  | 32.5       | (29-44)                                 |
| weight (kg)  | 66.2       | (56.0-78.5)                             |
| gestational age (weeks)                                  | 34.1       | (32.7-35.3)                             |
| CD4+ cell count (cells/ $\mu$ L)                         | 240        | (151-837)                               |
| HIV-1 RNA <50 cps/mL                                     | 4 out of 5 | (1 ptnt 242 cps/mL;<br>1 ptnt missing)  |
| other ARVs TDF / FTC / ZDV /<br>3TC / DRVr / LPVr / ATVr |            | 5 / 4 / 1 / 1 / 4 / 1 / 1               |
| race (black / caucasian)                                 | 3 / 3      |   |
| Delivery (n=5)   |            |   |
| gestational age (weeks)                                  | 37.8       | (34.1-38.7)                             |
| HIV-1 RNA <50 cps/mL                                     | 3 out of 5 | (1 ptnt 99 cps/mL;<br>1 ptnt 62 cps/mL) |
| way of delivery (caesarian section<br>/ natural)         | 4 / 2      |   |
| Post partum (n=5)  |            |   |
| weight (kg)  | 63.2       | (56.0-70.0)                             |
| weeks after delivery                                     | 8.6        | (4.6-12.9)                              |
| Infant   |            |   |
| infant weight at birth (g)                               | 2970       | (2030-3360)                             |
| infant VL undetectable                                   | 5 out of 5 | (1 child not known)                     |

Values are n for categorical variables and median (range) for continuous variables.

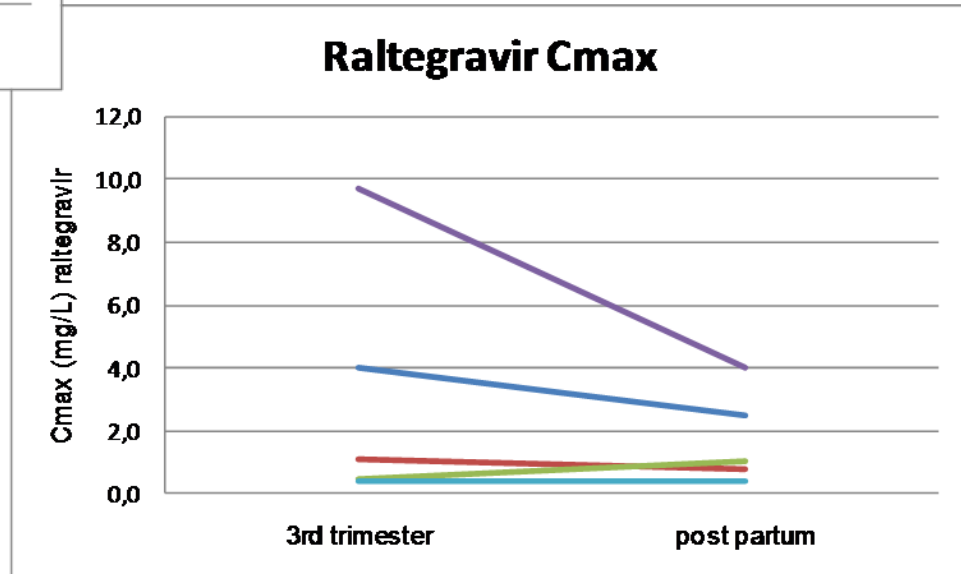
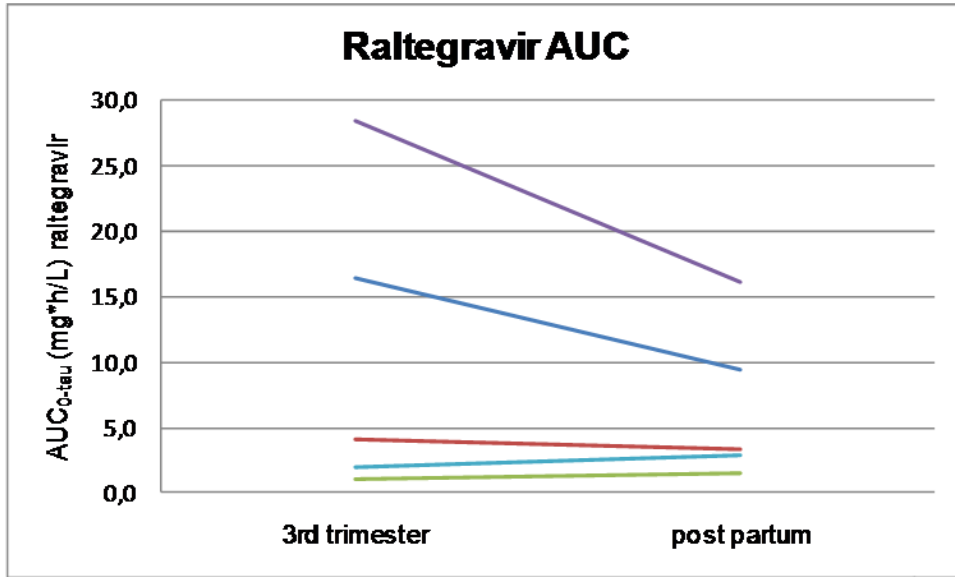
# First preliminary results

Raltegravir PK parameters

|                                     | 3rd trimester<br>(n=6)              | post partum (n=5)          | ratio (n=5)                              |
|-------------------------------------|-------------------------------------|----------------------------|--|
| <b>AUC<sub>0-12h</sub> (mg*h/L)</b> | 4.14 (1.85-28.32)                   | 5.42 (2.92-16.02)          | 1.26 (0.66-1.77)                         |
| <b>C<sub>12h</sub> (mg/L)</b>       | 0.09 (0.02-0.33)                    | 0.15 (0.05-0.28)           | 1.61 (0.21-2.33)                         |
| <b>C<sub>max</sub> (mg/L)</b>       | 0.79 (0.38-9.67)                    | 1.04 (0.44-4.03)           | 1.44 (0.44-2.40)                         |
|                                     | conc maternal at<br>delivery (mg/L) | conc. cord blood<br>(mg/L) | cord blood /<br>maternal plasma<br>ratio |
| <b>GB0201</b>                       | 0.615                               | 0.628                      | 1.02                                     |
| <b>IT0103</b>                       | 0.063                               | 0.073                      | 1.16                                     |

Values presented as median (range)

# First preliminary results



Presented as poster on the HIV-PK workshop April 2011

# First preliminary results

## Conclusion

- In this small population (n=6) exposure to raltegravir was not lower during pregnancy (third trimester) than post-partum. This is in contrast to a number of other antiretroviral agents, especially protease inhibitors.
- Raltegravir efficiently crosses the placenta.
- These results need to be confirmed in a larger group of patients.

## Sponsors

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

## Contact details

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