

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

Investigators meeting in Belgrade 13-Oct-2011



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

6th PANNA Investigators Meeting: Belgrade, Oct 2011

Agenda PANNA investigator meeting

13 October 2011

- Welcome & introduction of attendants
David Burger 17:30 - 17:40
- General introduction and update including first results and questions / problems to be solved from investigators
Angela Colbers 17:40 – 18:10
- Future plans: PIANO
David Burger 18:10 – 18:20
- Questions and closure
David Burger 18:20 – 18:30

Thanks to the sponsors of PANNA

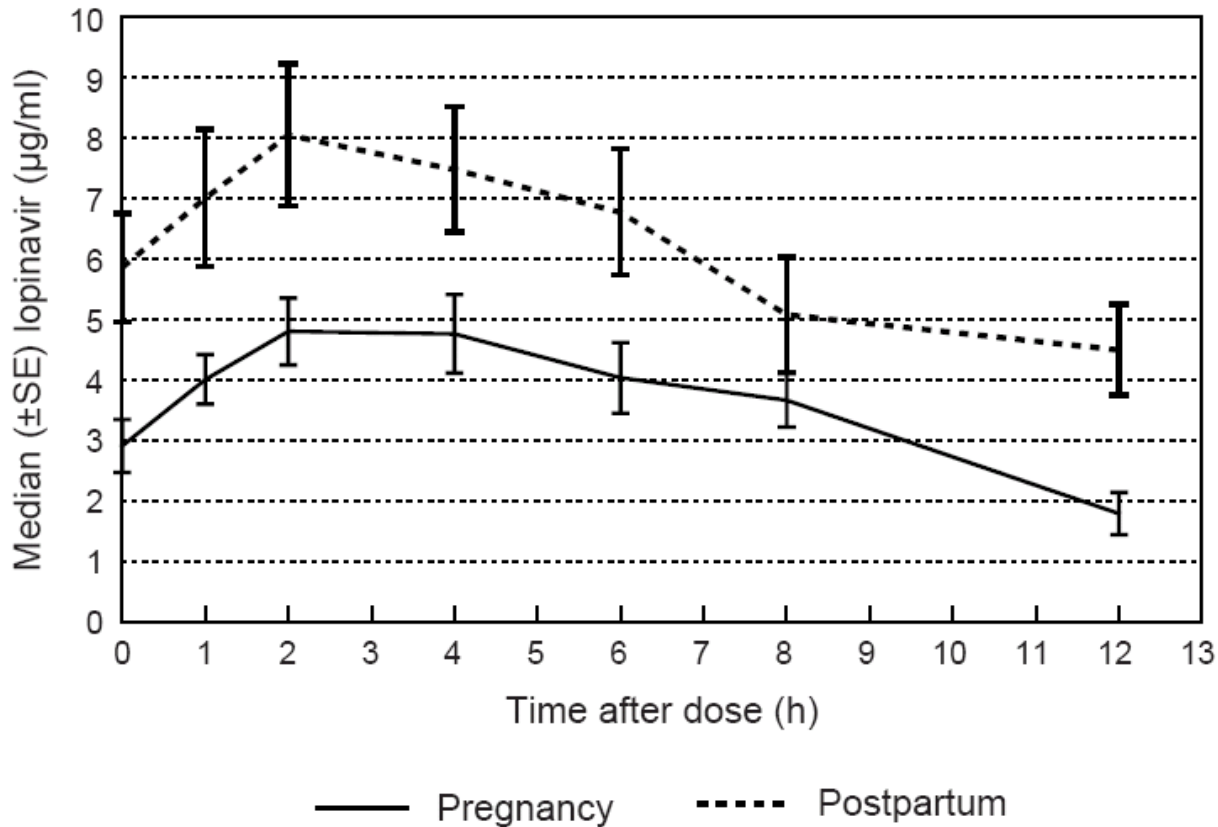
- NEAT/PENTA
- Merck
- BMS
- CTN (Canada)
- Negotiations with other companies are ongoing

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 maximize 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 Cotterⁱ and Jennifer S. Read^j
 for the PACTG 1026s study team*



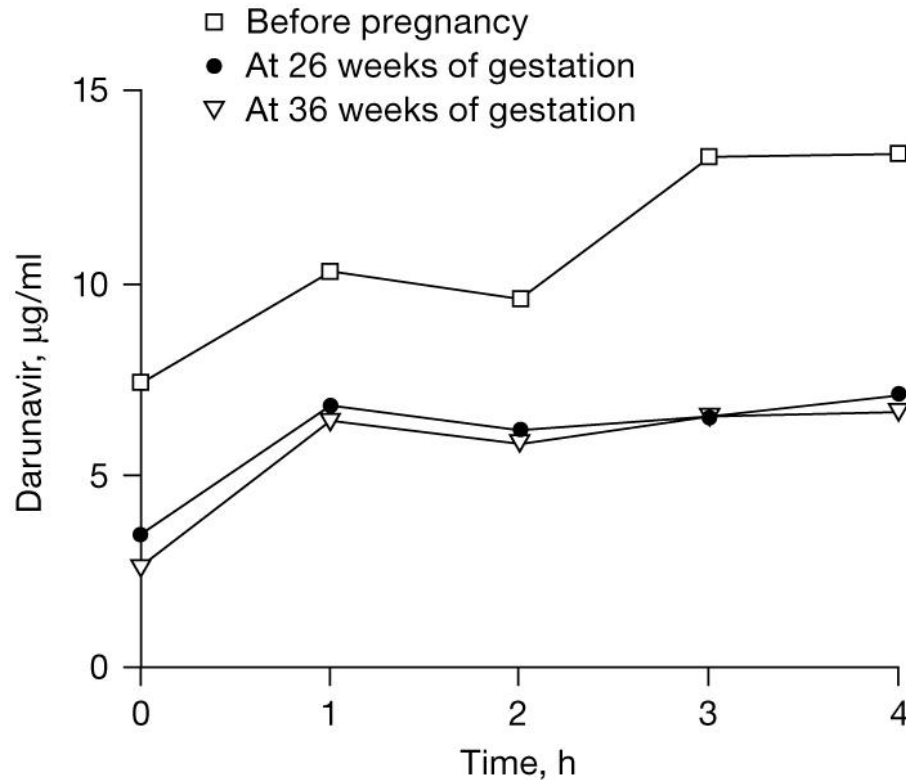
AUC: -28%
 Cmin: -56%

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**, *Enrica Tamburrini¹*, *Enzo Ragazzoni²*, *Andrea De Luca¹*, *Pierluigi Navarra²*



AUC: -45%
 Cmin: -61%

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States

September 14, 2011



Revisions to the May 24, 2010 Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV-1-Transmission in the United States have been made by the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 6 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy [†]	Concerns in Pregnancy
Preferred Agents					
Lopinavir + Ritonavir (LPV/r) Kaletra	<p>Tablets: (LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg)</p> <p>Oral solution: Each 5 mL contains (LPV 400 mg + RTV 100 mg)</p> <p>Oral solution contains 42% alcohol</p>	<p>LPV/r 400 mg/100 mg BID</p> <p>Third trimester: Some experts recommend increased dose LPV/r 600 mg/150 mg BID in third trimester</p> <p>With EFV or NVP (PI-naïve or PI-experienced patients): LPV/r 500 mg/125 mg tablets BID (use a combination of two LPV/r 200 mg/50 mg tablets + one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.) or LPV/r 533 mg/133 mg oral solution (6.5 mL) BID</p> <p>Tablets: Take without regard to meals.</p> <p>Oral solution: Take with food.</p> <p>Not used in pregnancy: Adult dosage of LPV/r 800 mg/200 mg once daily is not recommended for use in pregnancy.</p>	<p>PK studies suggest dose should be increased to 600 mg/150 mg BID in second and third trimester, especially in PI-experienced patients. If standard dosing is used, monitor virologic response and LPV drug levels, if available. Once-daily LPV/r dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.</p>	<p>AUC decreased in second and third trimester with standard dosing³¹⁻³³. AUC with dose of LPV/r 600 mg/150 mg twice daily in third trimester in women in the United States resulted in AUC similar to that in nonpregnant adults taking LPV/r 400 mg/100 mg dose twice daily¹². Low placental transfer to fetus.</p>	<p>No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)⁴. Well-tolerated, short-term safety demonstrated in Phase I/II studies.</p>

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 INCLUSION STOPPED**
- **Tenofovir (class B) 245mg QD INCLUSION STOPPED**

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

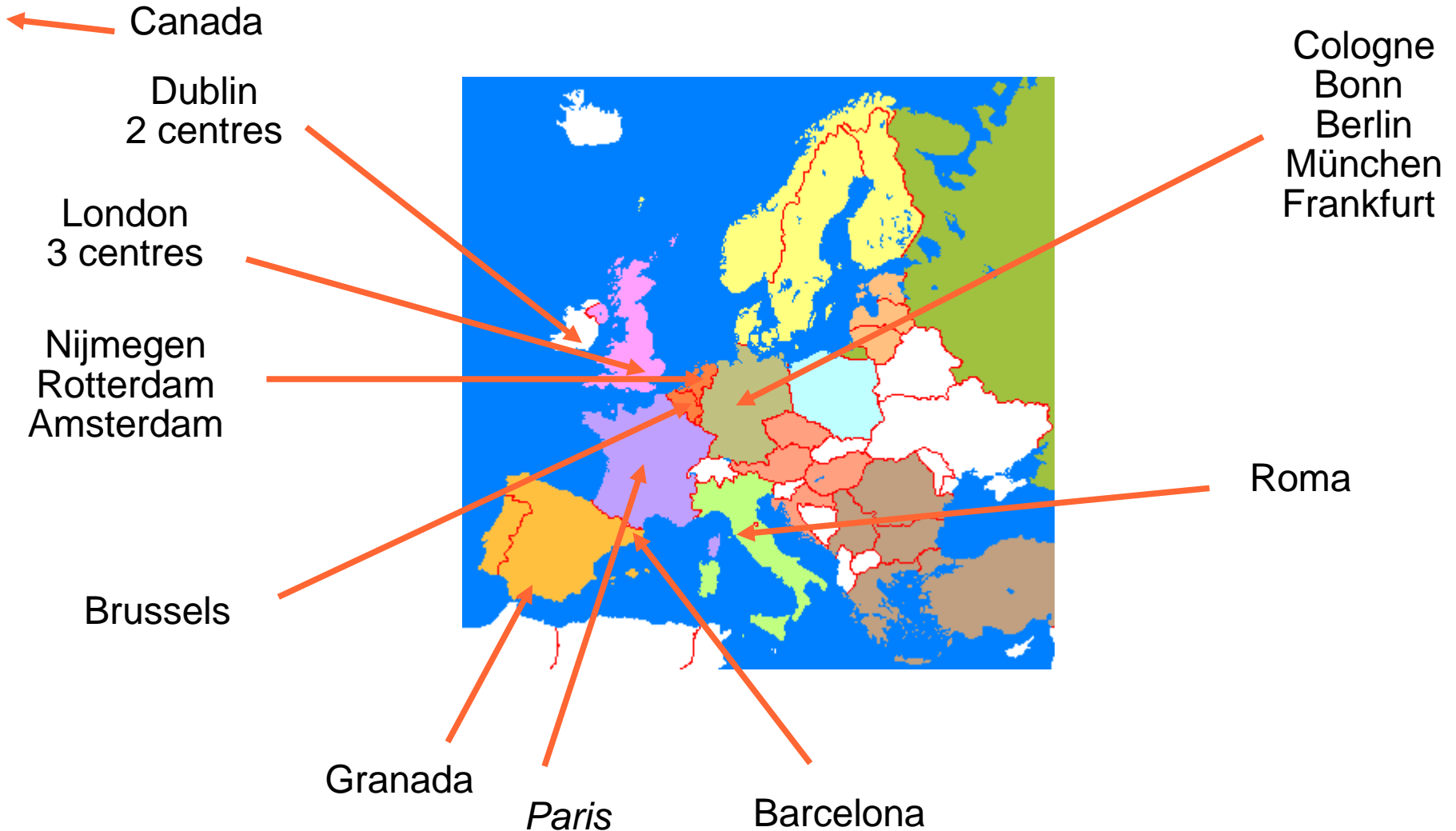
- Enfuvirtide (class B) 90mg BID
- Maraviroc (class B) 300mg BID

- To be added end of 2011:
- Rilpivirine and elvitegravir

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





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



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Home Contact

PANNA study
Inclusion
Study centres
Participate as a new study centre

PANNA network

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.

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Disclaimer Sitemap

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

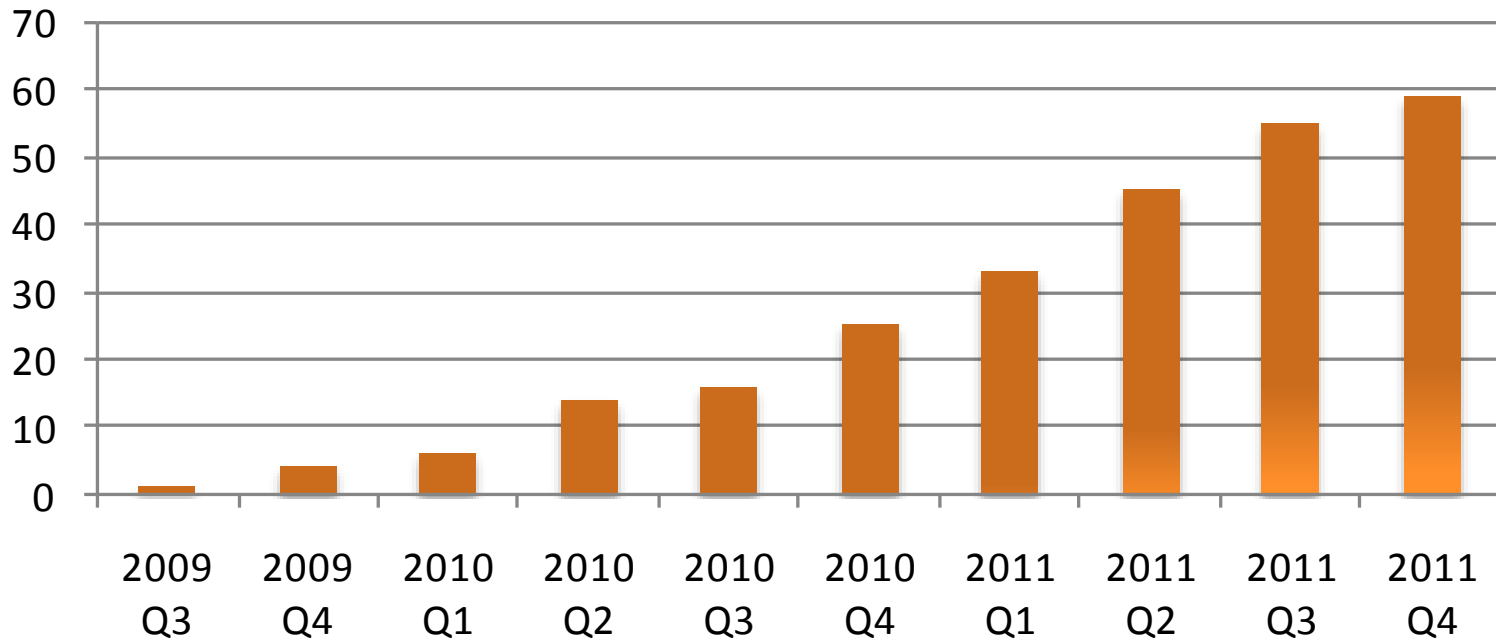
Drug name	Class	Dose and frequency	# pt included	# patients needed (16-#included)
Efavirenz, Stocrin®, EFV	NNRTI	600mg QD	1	15
Etravirine, Intelence®, TMC125	NNRTI	200mg BID	1	15
Emtricitabine, Emtriva® or FTC	NRTI	200mg QD	28	0
Tenofovir, Viread®, TDF	NtRTI	245mg QD	31	0
Atazanavir, Reyataz®	PI	300/100mg RTV QD 400mgQD 400/100mg RTV QD	15	1
Fosamprenavir, Telzir®, FPV	PI	700mg/100mg RTV BID 1400mg/200mg RTV QD	2	14
Darunavir, Prezista®, TMC114	PI	600mg/100mg RTV BID 800mg/100mg QD	15	1
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	8	8
Enfuvirtide, Fuzeon®	entry inhibitor	90mg BID	0	16
Maraviroc, Celsentri®	entry inhibitor	300mg BID	1	15

Status and milestones

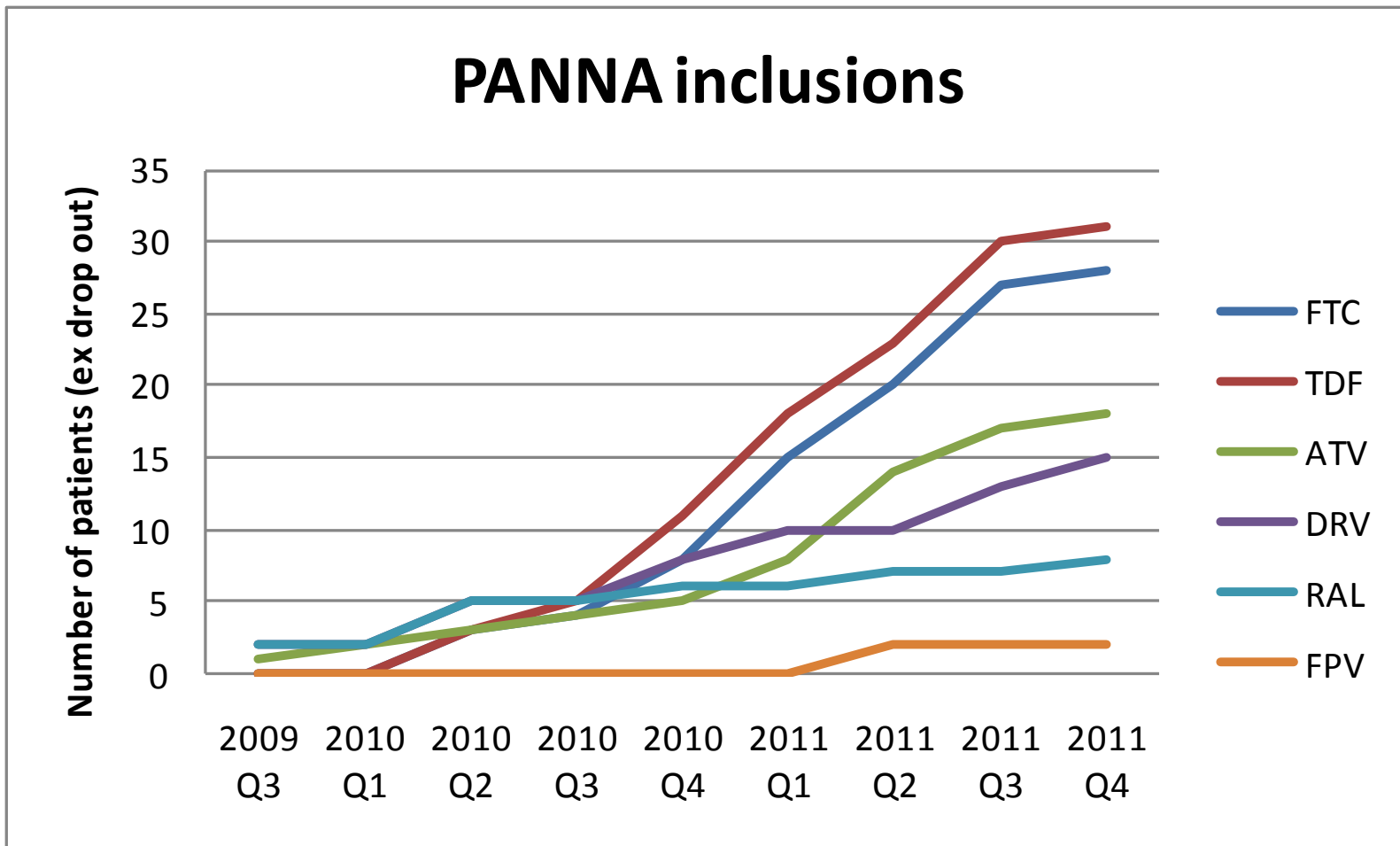
- The Netherlands, Spain, Italy, UK, Germany, Ireland, Belgium open for inclusion
- Canada: contract being worked on
- December 2012 TARGET:
 - For 5 drugs: data from 16 patients
 - Other agents: 5-10 patients
- October 2011:
 - Included 59 patients; 7 dropped out prior to first curve; 4 did not have a post partum curve
 - 9 compounds; inclusion for TDF and FTC closed

Status and milestones

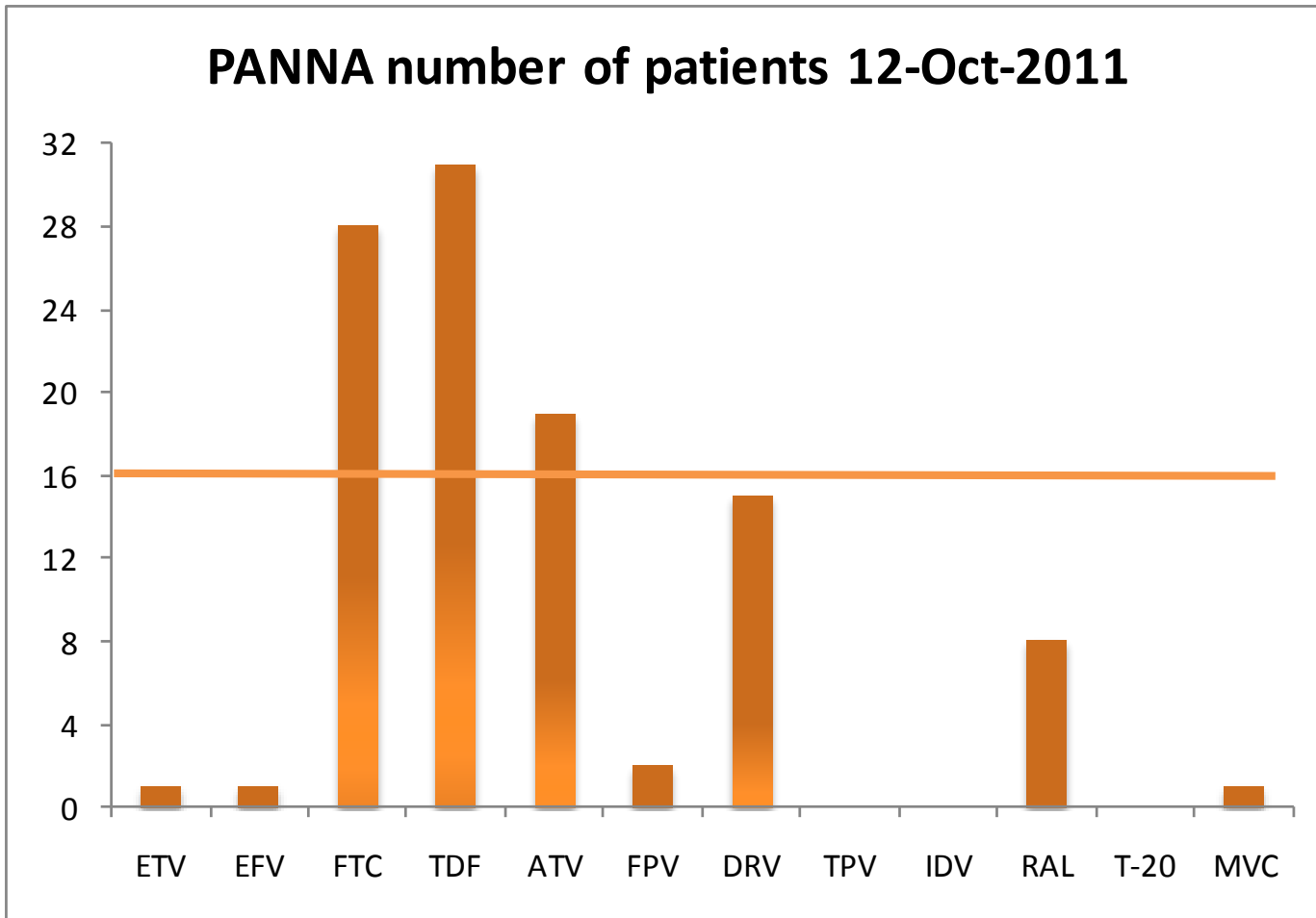
PANNA number of patients (cumulatively)



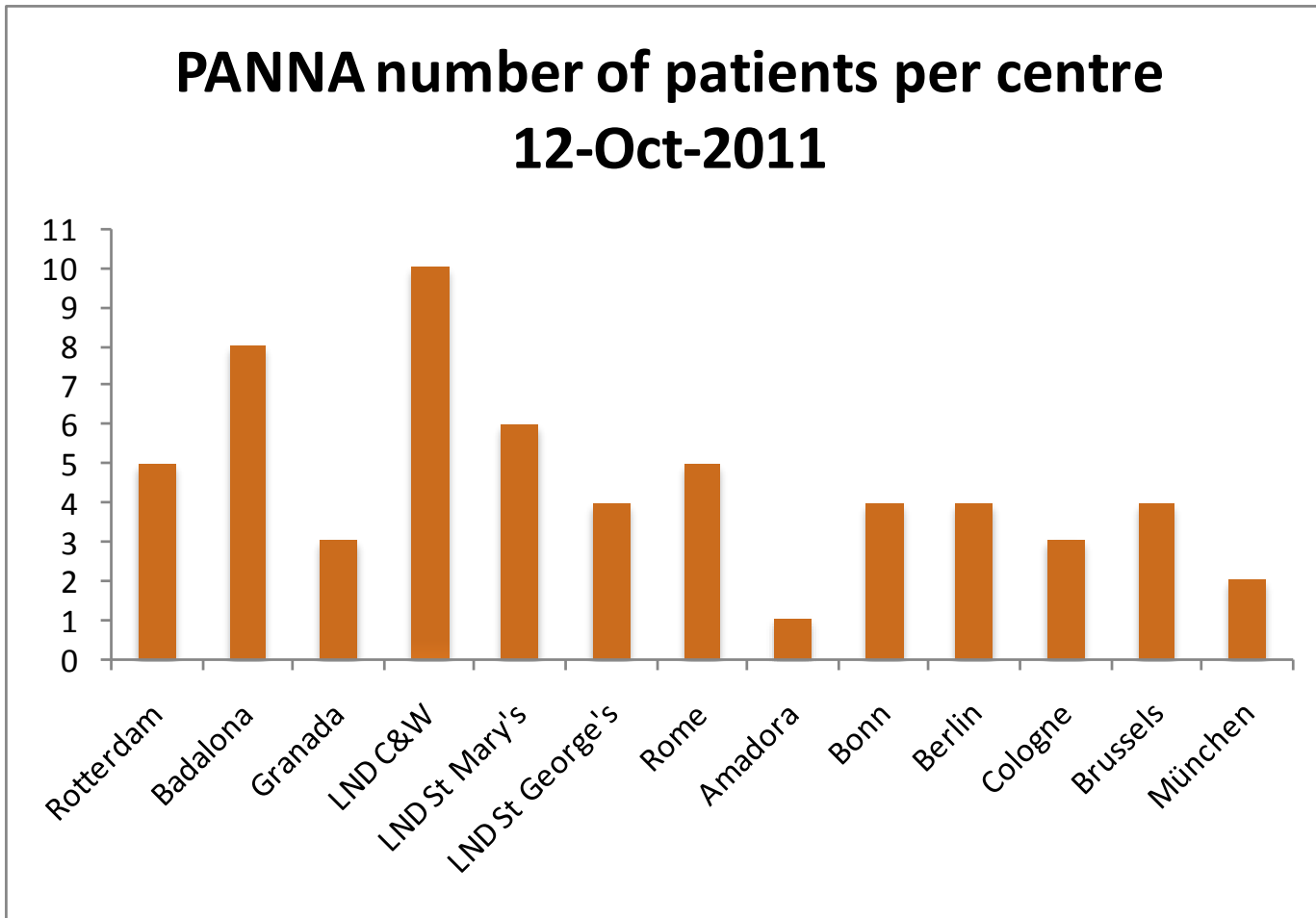
Status and milestones



Status and milestones



Status and milestones



Preliminary results

CONFIDENTIAL

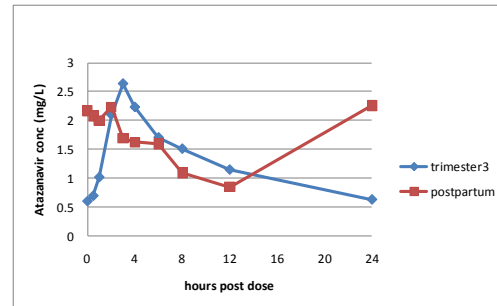
**Abstract on darunavir, atazanavir and ritonavir
submitted to CROI**

**Results are still confidential and not included in
the public presentation.**

Angela will send them to you on request.

Discussion

- 24h sample: to be taken in case of QD regimen of the medication under investigation
- Instruct the patient not to take medication before the 24h sample the next day



- 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.

Discussion

- Logistics regarding cord blood sampling

Examples of how to arrange it. Different for each site. This might be of more importance for the future.

- 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.

- 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: **Prof** David Burger:
D.Burger@akf.umcn.nl