Paediatric European Network for Treatment of AIDS (PENTA) since 1993

Since 2004 Penta Foundation
PENTA - AIMS

- To build a network of paediatric centres to undertake multicentre trials in a timely manner
- To address therapeutic questions specific to HIV infection in children which cannot be assumed/answered by trials in adults
- By collaboration and contact between paediatricians, often in small centres, to improve the levels of diagnosis and clinical care available to HIV infected children in Europe
- To expand the network to countries where ART therapy is being used in children
- To complement US and adult trials
Why the PENTA Network?

• PENTA aims to address questions:
  - which would otherwise not be addressed by the pharmaceutical industry (strategic questions)
  - Which require separate evaluation in children
  - Which require relatively large numbers of children
  - Includes collaboration with other networks and countries outside Europe

• Trials and Cohort studies are complimentary:
  - Involve the same groups of paediatricians
PENTA Trials -completed

Most have evaluated antiretroviral therapies, and have been randomised and blinded. LTFU is continuing

• Strategic:
  – when to start monotherapy - PENTA 1
  – Role of resistance testing – PENTA 8
  – TDM strategy evaluation – PENTA 14

• PK, Toxicity and tolerability
  – PENTA 3 - ZDV+ddC vs ZDV alone
  – PENTA 4 - 3TC vs placebo added to mono or dual NRTI ART
  – PENTA 13 - PK of twice versus once daily 3TC and Abacavir in children

• Activity & Toxicity of new combinations
  – PENTA 5 - ZDV+3TC vs ZDV+ABC vs 3TC+ABC
    - NFV vs NFV placebo

• PENTA 7 - PK and activity of early ART in infants

Most trials have included immunology, virology, adherence, substudies
PENTA Trials - ongoing and Planned in Europe

• Strategic:
  – **PENTA 9** (PENPACT1) - What to start with; when to switch
  – **PENTA 11** - Structured Treatment interruptions (LTFU)
  – **PENTA 16** – Short cycle therapy
  – **PENTA 17** – Simplification strategy (kaletra OD)
  – **PENTA 20** – NRTI sparing strategies in PI naïve children

• Pharmacokinetics:
  – **PENTA 15** - PK of twice versus once daily 3TC and Abacavir in infants (completed)
  – **PENTA 18** – PK new Kaletra paediatric formulation
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PENPACT 1
1st collaborative PENTA & PACTG trial
(PENTA 9 / PACTG 390)

A randomised clinical trial to compare different strategies of starting and changing antiretroviral therapy in previously untreated children in terms of long term virological suppression.
• What to start with

• Second randomisation - switch at VL
  >1,000 vs. >30,000 copies/ml
PENTA 18 Trial
(in collaboration with ABBOTT)

A study of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in HIV-1 infected children.
PENTA/ECS network

Clinical Trial Network
- PENTA trials
- NEAT

Cohorts:
- ECS
- HPPMCS
- Cohere
- Cohort coll.
- Postmark surv
- 3C4kids.
ECS: background

- An epidemiological study of HIV-infected pregnant women and MTCT, incorporating a birth cohort of infected and uninfected children, established in 1985
- Currently including around 9,500 mother-child pairs
- ECS network includes clinical sites in 10 countries in Western Europe (Belgium, Denmark, Germany, Italy, the Netherlands, Spain, Sweden, UK), Central Europe (Poland) and Eastern Europe (Ukraine [since 2000]; Kazakhstan commencing enrolment in 2009)
- Overall coordination is based at UCL Institute of Child Health, with the Eastern European coordination led by the Perinatal Prevention of AIDS Initiative
- Core epidemiological study, plus nested and supplementary studies, including European Paediatric HIV and Lipodystrophy Study and Ukraine Cohort of HIV-infected childbearing women
Epidemiology Studies and Cohort Collaborations

Complement trials by:

- Addressing questions at a population level
  - Effect of HAART
  - Long-term side-effects including lipodystrophy
- Assist with long-term follow-up of trials
- Provide data to:
  - explore questions to be addressed by trials
  - inform trial design
- Pharmacovigilance studies
PENTAG / ECS achievements

PENTA

• Unique paediatric clinical trial network
• More than 1500 children enrolled in trials to date
• Major contribution to ART registration for children (e.g. 3TC, ABC, Kaletra etc)
• Paediatric HIV guidelines
• 32 major papers in peer-reviewed journals

ECS

• Findings have contributed to development of evidence-based guidelines and of clinical trials
• 84 publications in peer-reviewed academic journals overall; 36 papers and conference presentations since start of 2006
• Provides the only epidemiological investigation of MTCT, HIV in pregnancy and paediatric HIV in Eastern Europe to date
PENTA/ECS network

Clinical Trial Network
- PENTA trials
- NEAT

Cohorts:
- ECS
- HPPMCS
- Cohere
- Eurocord
- Cohort coll.
- Postmark surv.
- 3Cs4kids

Pregnancy studies
- ECS
- PK (PANNA)
- Toxicity
- etc

Training:
- tr@inforPedHIV
- African training
- ACTIVATE
A European clinical pharmacology network to investigate the Pharmacokinetics of antiretroviral Agents in HIV-infected pregnant women (PANNA)
Tr@inforPedHIV 2009 - Zimbabwe

**Distance learning Residential Course**
9 modules on paediatric HIV topics
Kampala 20th - 22nd January 2009

- Basic epidemiology, virology and immunology
- Mother to child transmission and prevention programmes
- Antiretrovirals: Principle of ART treatment and strategies, guidelines, toxicity and resistance
- Opportunistic infections, management and prevention (including Hepatitis coinfection, TB coinfection)
- HIV and nutrition
- Psychosocial aspects: Including family issues, learning about HIV, adolescents with HIV
- An additional module covering issues specific to an African setting

**Registration fees:** distance learning + Residential Course: £

(Registration includes: memory stick with course modules, participation in the 3-day symposium, final CME certificate, and accommodation per diem support. Please note - transport not included)

To register contact: ?
For further information: Sabrina sac@ctu.mrc.ac.uk or www.aneca.org www.pentrials.org www.espid.org

Delegates at the 2007 Tr@inforPedHIV course in Kampala found it a very useful update and a practical approach to managing HIV in children. The course is appropriate for trained paediatricians looking after HIV positive children, trainee paediatricians, specialist nurses, pharmacists and dieticians.
PENTA Training activities

Europe:
- ESPID/PENTA integrated distance and residential learning courses since 2005 (more than 500 participants from 28 countries)
- ACTIVATE (Hungary, Belarus, Scotland)

Africa:
- Cameron March 2007
- Uganda December 2007
- Zimbabwe January 2009
- Ghana/Togo December 2009

Latina:
- Salvador Spring 2008
- Argentina August 2009

Asia:
- Thailand November 2008
PENTA/ECS network

Clinical Trial Network
- PENTA trials
- NEAT

Cohorts:
- ECS
- Eurocord
- Cohort coll.
- Postmark surv.

Pregnancy
- ECS
- PANNA/PK
- Toxicity
- etc

Training:
- tr@inforPedHIV
- RLS training
- ACTIVATE

Biobank
Pharmacology Ctee
Viro/immuno Ctee
Clinical Trial Centres
DSMB
Statistical team
IT support team
Training evaluation team
PENTA/ECS
Network Management structure

**ECS Steering Committee**

- **Cohort Collaboration Executive Committees**
- **PENTA/ECS Project Management Team**

**PENTA Executive Committee**

- **Data Safety Monitoring Committee**
- **Coordinating Committee Trial A**
- **Coordinating Committee Trial B**

**PENTA Steering Committee**

- **Training Committee**
- **Pharmacology Committee**
- **Virology Immunology Committee**

**Trial Centres:**
- **MRC CTU** coordinates centres from UK, Ireland, Netherlands, Italy, Germany, Sweden, Austria, Brazil, Thailand, Australia, Poland, Russia and Ukraine
- **INSERM/ANRS** coordinates centres in France, Belgium, Spain, Switzerland, Portugal, Argentina and Romania.

**Clinical Site Investigators**
Paediatric clinical centres participate in the PENTA Network and enrol children in clinical trials.
## PENTA Foundation 2006 – 2010 funding

**European Commission:**
- PENTA/ECS (FP6) - coordination
- PENTA LABNET (FP7) - coordination
- ACTIVATE (DG SANCO) – coordination
- NEAT – Partner
- CHAIN – Partner

**MRC, INSERM/ANRS, Italian Institute of Health, national AIDS program**

**Pharmaceutical companies for specific projects**

**NICHD (PENPACT 1)**

**Training activities**
New European Scenario for PENTA

- Less children born with HIV infection in Western Europe
- Growing epidemic in Eastern Europe (women and children)
- Vertically infected children are becoming young adults (..and transition to care is not always easy ..)

EU paediatric regulation
WHO ARV paediatric formulation “document”
PENTA network beyond “just” running clinical trials
Penta: strategic plans for the future

- Collaboration with adults HIV networks (Eurocoord, Neat, Chain)
- Collaboration with other PID networks in Europe ("incubator" for PENTi) and the US
- Extend collaboration to mid developed and developing countries (EDCTP)
- Collaboration with the EMEA (PENTA is represented within the PDCO)
- Participation to the European Network for “Medicine for Children” - TEDDY
- Implementing training/education programs for developed and developing countries on clinical research