PENTA-ID network:

How we move from HIV to other ID and pediatric medicine

Carlo Giaquinto
University of Padova, Italy

HISTORY and MISSION

Paediatric European Network for Treatment of AIDS (PENTA)

(www.penta-id.org)

- Established in 1991 as collaboration between paediatric HIV centres in Europe. Aim: to undertake independent clinical trials to address questions about antiretroviral therapy (ART) in HIV infected children where answers cannot be extrapolated from trials in adults

- Activities: not just clinical trials, but cohort studies collaboration, pregnancy studies and training/ educational programmes.

- Funding comes from:

- EC (10 projects coordinated by PENTA since Biomed 1, involvement in more than 20 EU funded projects)
- MRC
- INSERM/ANRS
- US-NIH (project-based), UNICEF etc
- Italian National Institute of Health (project-based)
- Pharmaceutical companies

MRC CTU, London:
Austria, Finland,
Germany, Ireland, Italy,
Netherlands, Sweden,
Poland, UK, Ukraine,(US)

Brazil, Thailand,
Bahamas, South Africa,
Uganda, Zimbabwe

INSERM SC10, Paris:
Belgium, Denmark,
France, Portugal,
Romania, Spain,
Switzerland

Argentina, Cameroon,
Mexico

PENTA 25 countries

>100 partners/sites

3 CTUs

PHPT
Thailand

PENTA HIV Trials -completed

Strategic:

- when to start monotherapy - PENTA 1
- Role f resistance testing – PENTA 8
- TDM strategy evaluation – PENTA 14
- What to start with – Penpact 1
- Treatment Interruption – PENTA 11

- 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 studies included immunolog, virlogy, QOL, adherence etc substudies

PENTA HIV Trials - ongoing

- **Strategic**:
  - **PENTA 11** - Structured Treatment interruptions (LTFU)
  - PENTA 16 (Breather)– Short cycle therapy
  - PENTA 17 (SMILE) – Simplification strategy (SOCvs INSTI/Dar)
  - PENTA 20 (Odyssey) – DLG first or second line

- **Pharmacokinetics:**
  - PENTA 15 - PK of twice versus once daily 3TC and Abacavir in infants
  - PENTA 18 (Koncert)– PK new Kaletra pediatric formulation

- **Research platform:**
  - EPIICAL: HIV functional cure

HISTORY and MISSION

The Foundation

- set up in 2004

- represents **the ideal legal and financially viable framework to run research and educational activities in different countries** in the field of Paediatric Infectious Diseases and Paediatrics in general

- a centre for **project development** and **project management (16 full time employees at the central office in Padova, 20 worldwide)**

- **involved in 15 proposals (6 as Coordinator) to the European Commission (FP7, IMI and H2020) from 2011 to 2016.**

- **unique expertise in running international research projects**

- **In 2015 a spin off company (PENTA-ID Innovation was set up to provide services to commercial entities.**

ODYSSEY

<18 years old,
Starting 1st line or switching to 2nd line
N = 700

First-line ART
N=310
Randomisation 1:1

stratified by
PI- or NNRTI (SOC),
NRTI backbone (all) and
routine VL availability

Second-line ART
N=390
Randomise 1:1

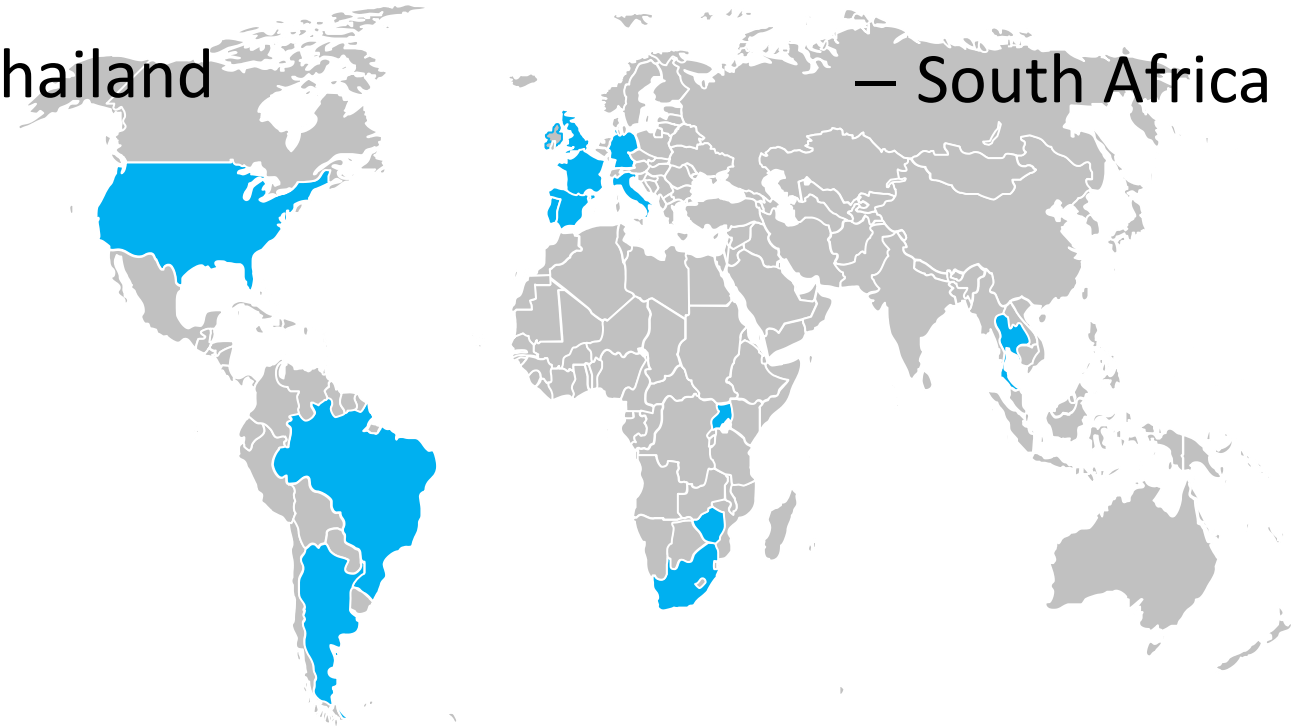
stratified by
PI- or non-PI (SOC),
NRTI backbone (all) and
routine VL availability

DTG ARM	SOC ARM	DTG ARM	SOC ARM
DTG + 2NRTI	bPI/NNRTI+2/3NRTI	DTG+2NRTI	bPI/NNRTI/Ral+2NRTI
155 patients	155 patients	195 patients	195 patients

Follow up: until last patient reaches 96 weeks
Endpoint: virological and clinical failure

Countries

- PENTA sites
  - Europe
  - South America
  - Thailand
- USA
- Africa
  - Uganda
  - Zimbabwe
  - South Africa



SMILE: Schematic Diagram

300 HIV-1 infected patients aged 6-18 years old *

- HIV-1 RNA viral load <50 c/ml for at least 12 months
- No evidence of lack of susceptibility to DRV or integrase inhibitors
- On a 3-drug PI/r or NNRTI containing regimen for at least 6 months.

* Children > 12 years old will be enrolled first

W0 = Randomisation

Arm 1 – NRTI sparing Once Daily INSTI+ DRV/r)
150 Children

Arm 2 – standard triple ART
150 Children

Follow-up

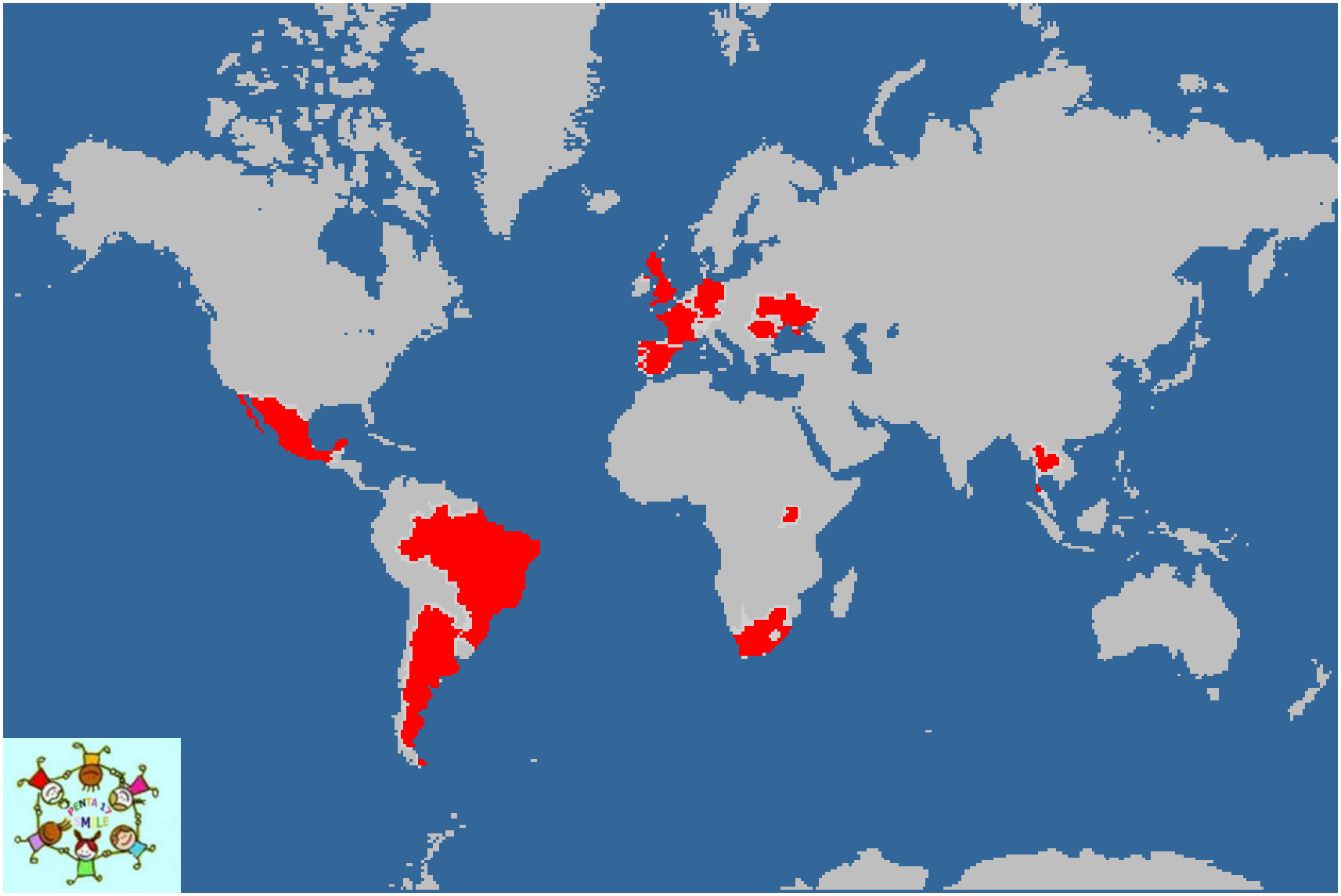
Clinic visits: W4,12,24,36,48

and every 12 weeks until the last patient reaches week 48 w.

Criteria to resume SOC regimen :

- **HIV-RNA ≥50 c/mL in two consecutive measures within 4 weeks (ideally within 1 week)**
- **New or recurrent CDC stage C or severe stage B event according to the toxicity grading for clinical events**
- **Pregnancy**
- **3 unconfirmed HIV-RNA >= 50 c/mL**

Participating Countries



From the initial focus on HIV to the broader area of Paediatric Infectious Diseases

- 2007: from PENTA to PENTA-ID

- **Focus on neglected and complex diseases**

EU funding:

- **NeoMero** (neonates)
- **NeoVanc** (neonates)
- **GRiP** ("medicine for children")
- **PREPARE** (prevention of epidemics)
- **EMIF** (creation of a European epidemiology/ICT platform)
- **COMBACTE-MAGNET** (molecules against Gram Negative infections)
- **GAPP** (clinical trials on "off-patent" drugs)
- **RESCEU (RSV)**
- **ZIKAction (ZIKA)**

- **Specific contracts and agreements with major International Paediatric Hospitals** not following up HIV positive children

- 2011: **PENTAid recognised by the EnprEMA as a level 1 Paediatric Clinical Trial Network in Europe** to conduct clinical trials in pediatric HIV, antimicrobials and vaccinology. **PENTA as PDCO member 2008 - 2014**

PENTA-ID Activities and main projects and fundings

HIV
- Trials
- Cohorts
- EPIICAL
- Pregnancy

Antimicrobials
- NEOmero/vanc
- COMBACTE
- PREPARE
- (G)ARPEC
- EPeMyn
- RESCEU

Hepatitis
- Cohorts
- Trials
- Pathogen

Ped medicine
- GRIP
- TEDDY
- ENPREMA
- EUPTCRI
- GAPP
- EMIF
- ZIKAction

Education
- HIV
- Other ID
- GRIP Mast

PENTA-ID Activities and main projects and fundings

HIV
- Trials
- Cohorts
- EPIICAL
- Pregnancy

EU (5%)
Pharma (75%)
PENTA F (20%)

Antimicrobials/virals
- NEOmero/vanc
- COMBACTE
- PREPARE
- (G)ARPEC
- EPeMyn
- RESCEU

EU (80%)
Pharma (?)
PENTA F (20%)

Hepatitis
- Cohorts
- Trials
- Pathogen

EU 0
Pharma (10%)
PENTA F (90%)

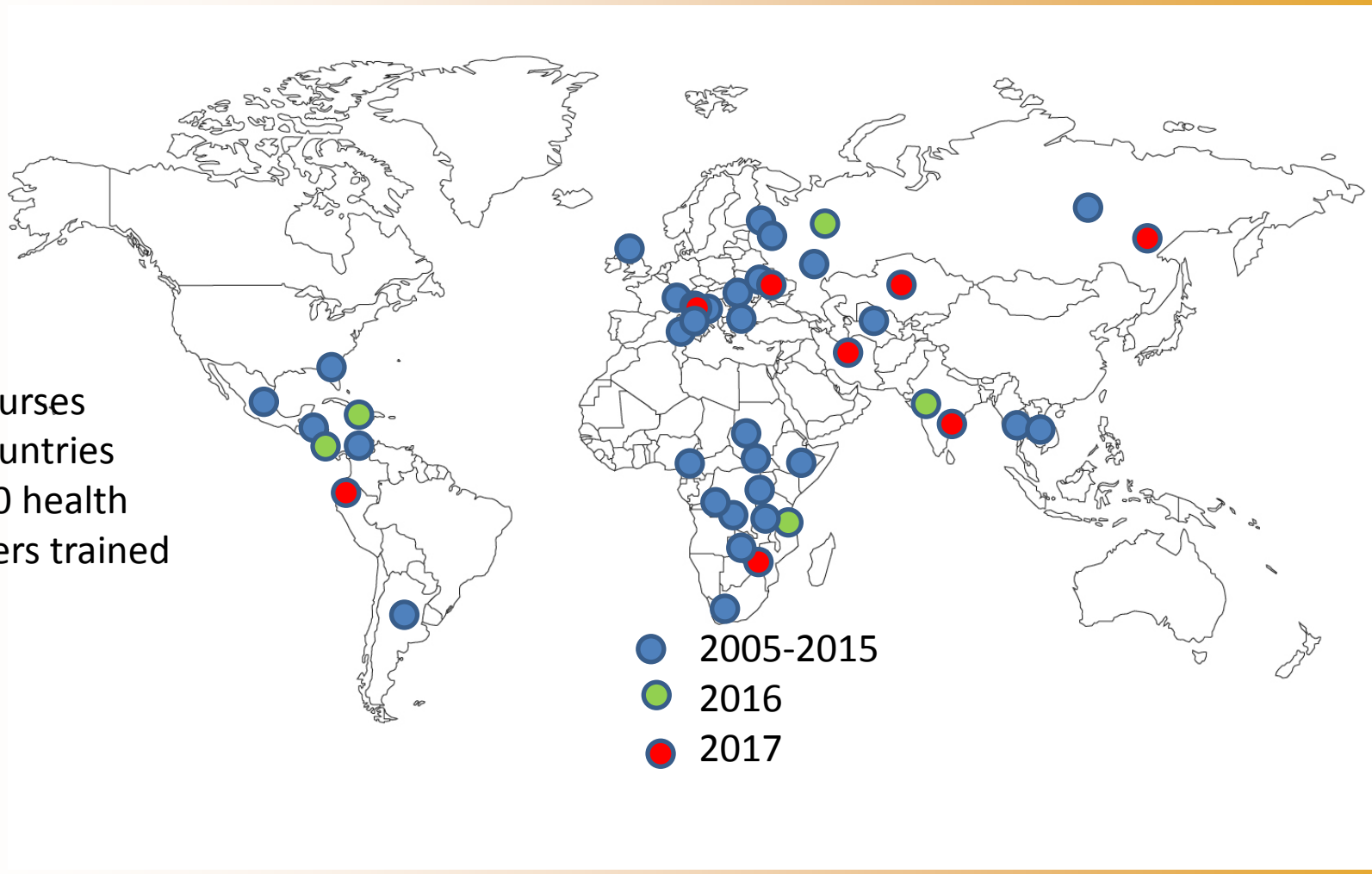
Ped medicine/others
- GRIP
- TEDDY
- ENPREMA
- EUPTCRI
- GAPP
- EMIF
- ZIKAction

EU (90%)
PENTA F (10%)

Education
- HIV
- Other ID
- GRIP Mast

EU (30%)
Pharma (30%)
PENTA F (20%)
UNICEF (20%)

TR@inforPedHIV 2005-2017



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

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

- ***20 sites from7 European Countries***
- ***14 agents studied***
- ***More than 150 women enriolled***