Final Publishable summary report

1.1 Executive Summary

PENTA-LABNET is a coordination action aimed at improving the range of products and clinical use of antiretrovirals (ARVs) in HIV-infected children in resource-rich and resource-limited countries. This has been achieved through building capacity of laboratories to undertake co-ordinated studies on pharmacokinetics, pharmacodynamics and pharmacogenetics of new formulations and dosing and studies of viral and immune responses to novel regimens and strategies for using ARVs in children. PENTA-LABNET forms a logical, necessary and cost-effective addition to the clinical-trial-focused research activities of the longstanding PENTA network, building on its existing operational infrastructures and expertise. To respond to emerging needs identified by EU as priority areas, the objective of PENTA-LABNET has been the development of a "drug centred" research platform, aimed at providing a complimentary range of activities focussed on supporting the rational selection of optimal dosage and delivery forms of ARVs, and providing the lab basis for evaluating new ARVs strategies in children. The definition, organisation and management of integrated pharmacological and viro/immunological studies to better characterise the concentration-exposure-effect relationship has been a central activity of PENTA-LABNET. In support of these studies, standardised data collection systems have been established enabling linkage of clinical and laboratory data. In addition a central biobank has been set up to provide rapid identification of samples to be used for research. The laboratory and paediatric expertise generated in PENTA-LABNET has supported and will support rapid assessment of new and existing individual and combined ARVs. The WHO has been a key partner of PENTA-LABNET to define research priorities in ARV drug development and (also through PENTA's extensive international links) to rapidly disseminate results to a range of stakeholders (e.g. EMEA and industries) and support the rapid translation of research findings into guidelines and practice for children in all settings.

1.2 Contractors involved

Acronym	Full Name	Country
PENTA	Fondazione PENTA – for the treatment and care of children with HIV - ONLUS	Italy
MRC-CTU	Medical Research Council	United Kingdom
INSERM-CTU	Institut National de la Santé et de la Recherche Medicale	France
RUN-MC	Radboud Universiteit Nijmegen – Stichting Katholieke Universiteit	Netherlands
UoL	The University of Liverpool	United Kingdom
UCL	University College London	United Kingdom
UL	Universiteit Leiden	Netherlands
AP-HP	Assistance Publique – Hopitaux de Paris	France

UNIPD	Università degli Studi di Padova	Italy
IRCCS S. Matteo	IRCCS Policlinico San Matteo – Istituto di Ricovero e Cura a Carattere Scientifico	Italy
PHPT	Institut de Recherche pour le Developpement	France
SoP	The School of Pharmacy, University of London	United Kingdom
WHO	World Health Organization	Switzerland

1.3 Co-ordinator contact details

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1.4 Summary description of project context and main objectives

PENTA-LABNET has its origin in the Pediatric European Network for the Treatment of AIDS (PENTA), originally funded by the EU. Laboratory investigators already involved with PENTA's clinical and epidemiological studies were grouped together for this project. Often, substudies of PENTA studies were not budgeted for and generally paid by Institutions themselves, which is not a good basis for building laboratory capacity within networks. PENTA-LABNET made it possible to support the work in the laboratories associated with a number of PENTA studies.

PENTA-LABNET represents a coordination action aimed at improving the range of products and clinical use of antiretroviral treatment (ART) regimens in HIV-infected children in resource-rich and resource-limited countries. This has been achieved through building capacity of laboratories to undertake co-ordinated studies on pharmacokinetics, pharmacodynamics and pharmacogenetics of new drug formulations and dosing regimens and undertaking studies of virological and immunological responses to novel strategies for using antiretroviral regimens in HIV – infected children.

PENTA-LABNET forms a logical, necessary and cost-effective addition to the clinical research activities of the longstanding PENTA/ECS network (see text box), building on its existing operational infrastructures (including systems for long term follow-up of children moving from PENTA trials to national cohorts, carefully documented specimen collections, etc) and world-class expertise of individuals. Before the implementation of PENTA-LABNET PENTA activities had mainly been focused on co-ordinating clinical trials in children to identify strategies for optimal use of antiretroviral therapy and on training and dissemination activities to improve management of HIV-infected children.

Although some studies had been done to identify appropriate dosing and combinations of drugs, PENTA had not conducted detailed investigations of more complex aspects of therapy, such as the integrated roles of virologic, immunologic, genomic and pharmacokinetic factors in response to therapy in children.

To respond to emerging needs identified by EU and WHO as priority areas, the objective of PENTA-LABNET was the development of a "drug centred" research strategy aimed at providing a

complementary range of activities focused on supporting the rational selection of optimal dosage and delivery forms of ARV agents, and new ARV drug regimen strategies for paediatric populations. The coordinating activities of PENTA-LABNET enabled implementation of this strategy.

PENTA/ECS

The Paediatric European Network for Treatment of AIDS (PENTA, www.pentatrials.org) was established in 1991 as a collaboration between paediatric HIV centres in Europe. The principal aim was to undertake clinical trials to address questions about antiretroviral therapy (ART) in HIV infected children where answers cannot be extrapolated from trials in adults. By 2010, more than 100 clinical centres in 21 countries in Europe, Asia, Africa and latin America and nearly 1500 children have been enrolled in 15 major CTs. Within the 6th FP, the coordination of the European Collaborative Study (ECS), one of the largest cohorts of children born to HIV positive mothers, has been integrated with PENTA, thus forming a single centralised European network for research on paediatric HIV. All PENTA activities are coordinated through PENTA Foundation.

By the beginning of PENTA LABNET effective triple-drug antiretroviral therapy (ART) had resulted in major reductions in mortality and morbidity in HIV-infected adults and children in industrialised countries. Most children were expected to survive well beyond adolescence and a number had already moved into adult care. As treatment is life-long and children were living into adulthood, long-term toxicity was an increasingly important consideration.

In adults the combination of ARV drugs into fixed dose combinations (FDCs) had led to ARV regimens that required fewer pills, increasing simplicity of programming, improving adherence and reducing prices; however less success had been achieved in the introduction of FDC and solid ARV preparations for children. This is in part because of the perceived complexity of dosing for children, and because dose delivered may require adjustments with age. The optimal ratio of individual ARV drugs within a FDC may also therefore need to vary based on age across childhood. The relative lack of pharmacokinetic and virological and immunological response data in children for individual drugs and ARV regimens makes recommendations on optimal combinations and products more difficult. Furthermore, age-related drug doses recommended at the time of drug licensing are often based on very limited data, particularly in younger children. Of note, changes to dosing recommendations based on post-licensing studies have either taken several years to be implemented (e.g. nelfinavir) or have not been implemented and appear only in paediatric guideline documents [US/PENTA/WHO guidelines].

Another important aspect is the maturation of the immune system in children, which results in faster disease progression and high levels of HIV viral load; however, paradoxically, children can repair damage to the immune system more readily than adults because they have a more active thymus.. Factors such as high pre-treatment viral load levels and increased thymic output in response to treatment need to be taken into account when assessing the relationship between PK parameters and response to antiretroviral drugs.

Therefore, there was a need not only to study new drugs for children through phase 1 studies thus ensuring timely access to novel therapies and agents for use in treatment experienced children who now survive, but to also improve the dosing forms of existing agents in order to facilitate adherence and reduce toxicity and to guide development of new strategies for optimal long-term use of ART in children, maintaining clinical efficacy and preserving future drug options while minimizing toxicity. Moreover, changes in drug disposition due to developmental and maturation processes across the wide age range from neonates to adolescents means that a model-based approach to establishing and validating dosing recommendations could be useful. PENTA-LABNET activities focused on addressing all these areas.

The PENTA network has taken the initiative, in response to the call for proposals of FP7, to add a new set of coordinating activities to its research focus, specifically aimed towards the better use of existing ARV drugs and development of new ARV agents for HIV infected children, through the establishment of a network of research laboratories (PENTA-LABNET) aimed at carrying out pharmacological,

immunological and virological studies to evaluate ARV drug doses and combinations to be used in HIV infected children.

Key elements for the success of this project are:

- The established strong collaborations of PENTA with the pharmaceutical industry (such as GlaxoSmithKline, Bristol-Myers Squibb, Abbott, Merck, Boehringer Ingelheim, Tibotec and Gilead) in order to undertake studies and apply research findings in paediatric drug development.

- Collaborative links between PENTA and studies on new fixed dose combination drugs manufactured by generic companies (e.g. CIPLA and the EDCTP-funded CHAPAS trials in Zambia)

- The established strong collaboration with WHO in defining the research agenda, providing both the international and public health perspective, building on international accepted norms and standards for research and laboratory practice. WHO will also guarantee a rapid translation and dissemination of research findings to international regulatory and policy making bodies, and treatment guidelines and clinical practices in resource limited settings.

The PENTA network provides an additional ideal setting for a rapid dissemination of the information among centres caring for HIV infected children. To avoid overlapping and duplications, PENTA-LABNET activities have been directly integrated with the existing clinical research activities coordinated by the PENTA Foundation (through a 6th FP funded CA).

Mission and objectives of PENTA-LABNET

The mission of PENTA-LABNET network was to serve as the platform for a number of coordinating activities to ensure that the studies undertaken are coordinated and together facilitate the development and early use of novel and improved paediatric ARV drugs for treating HIV infected children.
PENTA-LABNET has set up and linked a pan-European network of Pharmacology, Virology and Immunology laboratories working on paediatric ARV treatment that will use common standards in pharmacokinetic (PK), pharmacogenetic, virology and immunology to undertake priority research studies.

1.5 Description of the main S&T results/foreground

The mission of PENTA-LABNET network was to serve as the platform for a number of coordinating activities to ensure that the studies undertaken are coordinated and together facilitate the development and early use of novel and improved paediatric ARV drugs for treating HIV infected children.
PENTA-LABNET has set up a pan-European network of Pharmacology, Virology and Immunology laboratories working on paediatric ARV treatment that use common standards in pharmacokinetic (PK), pharmacogenetic, virology and immunology to undertake priority research studies.

As usual in this kind of projects, the Work was divided over a number of Workpackages (WP).

WP1 had in total 5 main projects with specific objectives: (1) To evaluate drug dosing regimens for children; (2) To set up a quality control program for therapeutic drug monitoring in children with HIV; (3) To evaluate pharmacokinetic and pharmacogenetic predictors of drug exposure; (4) PK/PD modeling to better characterize concentration-response relationship; (5) New bioanalytical methods for PK sampling.

WP1 has been remarkably successful in bringing together researchers from various laboratories in working together on combined datasets and >10 scientific papers have come out or are currently being drafted. And it is expected that another 5 papers will be completed after the end of the project.

The main results include:

- A match between the Liverpool TDM database and UK CHIPS cohort revealed 901 TDM results. A trend was visible of increased uptake of TDM in the period 1999 – 2006 although at the end of the period still only approximately 12% of children received TDM. A feasibility survey of the Dutch HIV Monitoring Foundation revealed 300 children of whom 85% had at least 1 TDM result in the database. The data are now being analyzed for a paper to be published after the end of the project (2013/2014).

- PK models for lamivudine and abacavir using data from PENTA 13, PENTA 15 and ARROW studies have been very successful and support once daily dosing of the nucleoside analogues lamivudine and abacavir in HIV-infected children between 3 months and 12 years old. Five publications on these analyses have been prepared .

- Pediatric exposure can be either predicted from adult data (as shown for saquinavir) or based on in vitro – in vivo extrapolation modeling techniques using SymCYP (efavirenz).

- During the duration of the project, an increase occurred of more PENTA LABNET laboratories to receive certificates for more ARVs. As a result, more laboratories are now qualified to participate in PENTA studies in the future. Still, performance of some other laboratories need to be improved, highlighting the necessity of maintaining the QC program also after the projects has ended. A paper on the 10 year experience with external proficiency testing was published in 2011 (Burger et al. Ther Drug Monitor 2011). A paper on the performance of Penta labnet laboratories vs. other laboratories is currently in preparation with 2013 as the expected year of publication.

- Combining data sets made it possible for the first time to evaluate the effect of maturation and body weight on lamivudine pharmacokinetics in a large data set ranging from neonates to adolescents (Bouazza et al. AAC 2011). Similar approaches have been followed for the HIV protease inhibitors atazanavir and lopinavir; this made it possible to evaluate recommended doses in children (Foissac et al. Br J Clin Pharmacol 2011; Urien et al. Br J Clin Pharmacol 2011).

WP2

The work in WP2 was centralized around one of the most important pediatric HIV studies in recent years: the PENTA 11 study on planned treatment interruption (PTI) *(Paediatric European Network for Treatment of AIDS. Response to planned treatment interruptions in HIV infection varies across childhood. AIDS 2010; 24: 231-241)*.

One main result of the study was that the CD4 nadir prior to the onset of ART was key to determining the CD4 count following ART interruption.

The PENTA 11 immunology and virology substudy was designed to explore the influence of PTI on the immunology and virology in more detail and could only be performed as part of this grant. Most of the work in the first part of the project was directed at standardization of assays between two laboratories (Padua & London); the second part could be used to analyze the samples.

The results show that in PTI in children is associated with rapid changes in CD4 and CD8 cells, associated with increased cell turnover and immune activation. These data also indicate that children off treatment may be able to maintain their naïve cell CD4 cells, at least in proportion to their memory cell pool, which will be important for CD4 cell recovery upon ART re-introduction.

Overall, these findings indicate that no adverse clinical, immunological or virological consequences of PTI were observed two years after end of PENTA 11 trial. While ART interruption is not generally recommended, it may be a safe option for children, particularly when there is high risk of unplanned treatment interruptions.

Ongoing 5-year follow-up of children in PENTA 11 will evaluate long-term immunological/ virological implications of PTI.

Furthermore, data from PENTA 5 trial has been mathematically modelled to enable prediction of immunological outcome after ART initiation. CD4 counts in perinatally HIV-infected, therapy-naive children were monitored following initiation of antiretroviral therapy (ART),for median 5.7 years. 127 children were studied (median(IQR) age 5.3(2.4-8.6) years; pre-ART CD4 count 620(343-912) cells

per ul). Older children had lower age-adjusted CD4 count in the long term and at treatment initiation ($p < 0.0001$). At all ages, lower count before treatment was associated with impaired recovery ($p < 0.0001$). Overall, it appears that the immature immune system can recover well from HIV infection, via the naive pool. However, this potential is progressively damaged with age and/or duration of infection (.Lewis J, Walker AS, Castro H, De Rossi A, Gibb DM, Giaquinto C, Klein N, Callard R. Age and CD4 count at initiation of antiretroviral therapy in HIV-infected children: effects on long-term T-cell reconstitution. J Infect Dis. 2012;205:548-56).

WP3

This WP focused on the establishment and maintenance of the PENTA LABNET biobank, an essential part of the network.

During the lifetime of the project we, as expected, noticed a significant decrease in number of discrepancies on the samples collected in the new trials (PENTA11 Long Term, KONCERT/PENTA 18 and BREATHER/PENTA 16) where we implemented the standard operating procedures, the standard laboratory requisition form and the pre-printed labels system. We now are ready for future PENTA trials (PENTA 17, PENTA 20).

The biobank is not only meant for storage but also for extraction and shipment to laboratories, for instance for substudies. Extraction for PENPACT1/PENTA9 (toxicity) and KONCERT/PENTA 18 (PK) have been successfully applied, among others.

The centralised database contains the information related to the samples and their location in the central biobank. This database contains currently data on 12175 PENTA samples (Plasma, Cells (pellets and viable), Serum) available for current and future research studies in accordance with GCP and ethic requirements.

The Clinical Trials Units have access to the central database through a website that allows the visualisation of all PENTA samples available by trial and by site. Many tools are provided on the website to improve data monitoring on samples.

WP4

The WP focusesd on centralisation of datasets within Penta Laboratories and Clinical Trial Units. To date few samples have been tested outside the PENTA trials and existing file specifications developed for PENTA trials have been sufficient for the analyses of these clinical data together with PK, resistance and immunology data.

However HICDEP is now a recognised format available for linking cohort and laboratory data. Ongoing work in EPPICC is able to benefit from the work involved in developing HICDEP.

Due to the lack of other cohort data, our work has focused on the UK and Ireland CHIPS cohort which was successfully linked to the UK HIV Drug Resistance Database. Soft linkage was performed between CHIPS and the UK HIV Drug Resistance database using an iterative algorithm based on pseudo-anonymised identifiers. The linkage enables the study of resistance patterns that emerge following exposure to specific drug regimens.

Training and Capacity building were the objectives of **WP5**. The purpose of this WP was to select laboratories who can perform analyses according to GCLP standards so that data can be used both for scientific research as well as for licensing purposes. One of the laboratories participating in the QC program has now been selected to perform PK analyses for the KONCERT (Penta 18) trial that will provide PK data for licensing purposes of pediatric Kaletra tablets by the EMA.QC training program carried out in several labs resulted in 4-7 labs who showed very good performances (depending on the analyte). This allows to carry out future PENTA PK studies (for instance P16, P17 and P20) using different labs and therefore optimizing the use of resources.

Quality control and capacity building carried out by virology and immunology labs. This resulted in joint studies as described in WP2 with presentation of results at the CROI.

Training and Capacity building beyond PENTA LABNET.

The knowledge generated by PENTA-LABNET PK and viroimmunolgical studies has been used in the development of the new WHO guidelines. The WHO partnership has been of great value in translating research into practice forming a logical gateway in disseminating knowledge.
Training including PENTA LABNET material was carried out to hundreds health care workers in developed and developing countries, including Africa, Latin/central America and Asia. During the courses face to face presentations were delivered by experts belonging to the PENTA LABNET network. Computer based modules were also delivered before or after the residential courses either via web (Rome) or providing CD/datastick including the HTLM or pdf modules. Modules on pharmacology, immunology and virology were very much appreciated by the trainees.

WP6 is on project management.
The management tasks implemented in the considered period, with respect to the Objectives to be pursued, are reported hereunder:

Day-to-day Management

Follow-up and monitoring project work plan and time schedule and implementation of corrective actions; liaison with the EC Project Officer on any legal, contractual, financial and administrative issues; internal communication within the Consortium.

Support for meetings organization both at the Executive Board and Governing Council levels, including the production of the corresponding minutes, was provided. PENTA LABNET meetings were organised during the bi-annual meetings of the PENTA Steering Committee. PENTA LABNET end meeting was held in June 2012 in order to discuss project results and any future plans.

Coordination of communications with other EU networks: TEDDY, EUROCOORD, NEAT, CHAIN, GRIP. PENTA LABNET established links with CHAIN, the EU funded network for studying antiretroviral resistance in adults and the WHO resistance program.

Reporting and Financial Management

Efficient financial monitoring was run, including allocation of the EC contribution following approval of the 1st and 2nd periodic report, cost control and justification, budget forecasting.

A grant agreement amendment was submitted to the Commission in order to request for both a budget reassignment based on a reassignment of tasks between beneficiaries and a project extension of three months.

Support was given to all network members to help with reporting and budgetary requirements. The first, second and third periodic report to the Commission have been prepared. Periodic and final reporting were included in the agenda and properly discussed at the PENTA LABNET end meeting that was held on 20th June 2012 in Paris the day before the bi-annual meeting of the PENTA Steering Committee.

Contract and Legal Management

This task deals with all contractual and other legal issues related to the project, including in particular Grant Agreement and Consortium Agreement implementation and amendments as well as partnership management (including third parties).

The above mentioned grant agreement amendment was approved by the Commission and the new approved Annex I (Description of Work) was circulated to all partners. New approved project end date is at month 51.

A Universal Transfer of Rights and Obligations (UTRO) occurred from The School of Pharmacy, University of London (SoP) to University College London (UCL) with effective date 1 January 2012. This change is included in the current approved version of Annex I, where the former beneficiary SoP disappears whereas beneficiary UCL is split between two 'units': the Institute of Child Health (ICH) and the Centre for Paediatric Pharmacy Research (CPPR), the School of Pharmacy.

Management tasks are carried out in accordance with Articles II.2.3 and II.16.5 of the Grant Agreement.

WP7 is on coordination and networking. PENTA-LABNET partners participated in WHO activities for the optimization of paediatric ART. These activities included the development of the normative guidance needed to improve and simplify ARV formulations for infants, children and adolescents, as well as the move towards harmonization with adult regimens, according to the principles established in the recently launched WHO/UNAIDS Treatment 2.0 strategy. This normative work was provided by the Paediatric Antiretroviral Working Group (PAWG), which was convened to discuss an optimal paediatric formulary to serve as guidance to national HIV programmes, procurement agencies, funders and drug manufacturers. In April 2011 the PAWG met in Geneva, Switzerland and defined the criteria for optimization and then evaluated all available paediatric products against these criteria. This process resulted in three related lists: optimal products, limited-use products and non-essential products. A meeting report was produced that presents the rationale of this discussion and the product lists for public comment (http://www.who.int/hiv/pub/meetingreports/paediatric_working_group/en/index.html). WHO and its partners committed to review and update the report periodically.

The PAWG also met in October 2011 to discuss and revise the dosing guidance for new and upcoming pediatric ARV formulations. In this meeting the PAWG focused on providing appropriate dosing of new ARVs by age group and weight-band, as well as advising on potential ratios of future paediatric fixed-dose combinations (FDCs). In addition, the group provided recommendations on the storage of lopinavir/ritonavir (LPV/r) syrup and on nevirapine (NVP) lead-in dosing. A meeting report on this activity was published in August 2012 (http://www.who.int/hiv/pub/meetingreports/paediatric_arv/en/index.html).

Finally, an advocacy toolkit on paediatric HIV treatment was developed by this working group to support efforts in advocating for increased commitment to, and resources for, pediatric HIV diagnosis, care and treatment in high HIV prevalence countries and regions (http://www.who.int/hiv/pub/pediatric_toolkit2011/en/index.html).

PENTA has also been directly involved in the collaboration with other EU funded networks and has played a key role in the work of EUROCOORD, first in the finalization of the proposal and then in the actual project activities. PENTA LABNET WP2 activities were also coordinated with the CHAIN activities regarding studies on ARV resistance.

PENTA is also participating in the NEAT project specifically in evaluating the PK of ARVs in pregnant women which has now enrolled more than 75 mothers (www.pannastudy.com). PENTA LABNET WP1 leadership had a major role on it. Also PENTA has been involved in activities of the Global Research in Pediatric (GRIP) Network of Excellence which has been funded by the European Commission aiming to facilitate the development of drugs in children.

Through its formal representatives (JP Aboulker and Alex Compagnucci) within the EMA PDCO PENTA has been directly involved in the evaluation and discussion of most Paediatric Investigation Plans regarding ARVs presented by pharmaceutical Companies.

Collaboration with major pharmaceutical companies was established.

1.6 Description of the potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and the exploitation of results

The PENTA LABNET group has held annual meetings (see minutes) where results were summarized to the Penta Steering Committee consisting of leading European paediatricians. In addition, results have also been communicated at the Penta Investigator's meeting, held every 2 years, where >150 paediatricians from Europe and other continents as well as representatives of pharmaceutical companies attend.

PENTA LABNET has been extremely successful in publishing its work in major scientific journals. It both highlights the quality of PENTA LABNET investigators as well as the clinical relevance of the work performed by its members. See below the total of 33 (!) papers:

1. Benaboud S, Ekouévi DK, Urien S, Rey E, Arrivé E, Blanche S, Gray G, Sim KL, Avit D, McIntyre J, Nerrienet E, Dabis F, Tréluyer JM, Hirt D; TEmAA ANRS 12109 Study Group. Population pharmacokinetics of nevirapine in HIV-1-infected pregnant women and their neonates. *Antimicrob Agents Chemother*. 2011 Jan;55(1):331-7. Epub 2010 Oct 18. PubMed PMID: 20956588; PubMed Central PMCID: PMC3019646.

2. Benaboud S, Pruvost A, Coffie PA, Ekouévi DK, Urien S, Arrivé E, Blanche S, Théodoro F, Avit D, Dabis F, Tréluyer JM, Hirt D. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. *Antimicrob Agents Chemother*. 2011 Mar;55(3):1315-7. Epub 2010 Dec 20. PubMed PMID: 21173182; PubMed Central PMCID: PMC3067089.

3. Bouazza N, Hirt D, Bardin C, Diagbouga S, Nacro B, Hien H, Zoure E, Rouet F, Ouiminga A, Blanche S, Van De Perre P, Tréluyer JM, Msellati P, Urien S. Is the recommended once-daily dose of lamivudine optimal in West African HIV-infected children? *Antimicrob Agents Chemother*. 2010 Aug;54(8):3280-6. Epub 2010 Jun 1. PubMed PMID: 20516271; PubMed Central PMCID: PMC2916343.

4. Bouazza N, Hirt D, Blanche S, Frange P, Rey E, Tréluyer JM, Urien S. Developmental pharmacokinetics of lamivudine in 580 pediatric patients ranging from neonates to adolescents. *Antimicrob Agents Chemother*. 2011 Jul;55(7):3498-3504. Epub 2011 May 16. PubMed PMID: 21576443; PubMed Central PMCID: PMC3122471.

5. Bouazza N, Urien S, Hirt D, Frange P, Rey E, Benaboud S, Foissac F, Blanche S, Tréluyer JM. Population Pharmacokinetics of Tenofovir in HIV-1 Infected Pediatric Patients. *J Acquir Immune Defic Syndr*. 2011 Aug 18. [Epub ahead of print] PubMed PMID: 21857359.

6. Bunupuradah T, Duong T, Compagnucci A, McMaster P, Bernardi S, Kanjanavanit S, Rampon O, Faye A, Saïdi Y, Riault Y, De Rossi A, Klein N, Ananworanich J, Gibb D on behalf of the PENTA 11 Extension Study Group. Outcomes after reinitiating antiretroviral therapy in children randomized to planned treatment interruptions in the PENTA 11 Study – *AIDS*. 2012 Nov 6. [Epub ahead of print] PubMed PMID: 23135172

7. Burger D, Pharma D, Teulen M et al. The International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma: A Global Proficiency Testing Program. *Ther Drug Monit* 2011;33:239–243.

8. Cella M, Gorter de Vries F, Burger D et al. A Model-Based Approach to Dose Selection in Early Pediatric Development. *Clinical Pharmacology & Therapeutics* 2010; 87(3):294-302.

9. Cella M, Zhao W, Jacqz-Aigrain E, Burger D, Danhof M, Della Pasqua OE. Paediatric drug development: are population models predictive of pharmacokinetics across paediatric populations? *Br J Clin Pharmacol*. 2011 Sep;72(3):454-64.

10. Doerholt K, Judd A, Bleier J, Foster C, Menson E, Sharland M et al. Atazanavir (ATV) use and dosing in HIV-1-infected children in the UK and Ireland. 30th Annual Meeting of the European Society for Paediatric Infectious Diseases, Thessaloniki, 2012 (oral abstract number A-435-0012-01125).

11. Donegan K, Doerholt K, Judd A, Lyall H, Menson E, Butler K, Tookey P, Riordan A, Shingadia D, Tudor-Williams G, Gibb DM, Walker AS. Lopinavir Dosing in HIV-infected Children in the United Kingdom and Ireland. *Pediatr Infect Dis J.* 2013 Jan;32(1):45-50. doi: 10.1097/INF.0b013e31827842c9. PubMed PMID:23076384.

12. Donegan K L, Walker A S, Dunn D, Judd A, Pillay D, Menson E, Lyall H, Tudor-Williams G, Gibb D M on behalf of the Collaborative HIV paediatric Study and the UK HIV Drug Resistance Database. The prevalence of darunavir associated mutations in HIV-1 infected children in the UK.

Antivir Ther. 2012;17(4):599-603. doi: 10.3851/IMP2015. Epub 2011 Dec 15. Erratum in: *Antivir Ther*. 2012;17(4):769. PMID: 22300840.

13. Foissac F, Blanche S, Dollfus C, Hirt D, Firtion G, Laurent C, Treluyer JM, Urien S.Foissac F, Blanche S, Dollfus C, Hirt D, Firtion G, Laurent C, Treluyer JM, Urien S. Population pharmacokinetics of atazanavir/r in HIV-1 infected children and adolescents. *Br J Clin Pharmacol*..2011 Dec;72(6):940-7. doi: 10.1111/j.1365-2125.2011.04035.x.PubMed PMID: 21649692.

14. Foissac F, Urien S, Hirt D, Frange P, Chaix ML, Treluyer JM, Blanche S. Pharmacokinetics and virological efficacy after switch to once-daily lopinavir-ritonavir in treatment-experienced HIV-1-infected children. *Antimicrob Agents Chemother*. 2011 Sep;55(9):4320-5. Epub 2011 Jul 11. PubMed PMID: 21746952; PubMed Central PMCID: PMC3165353.

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The societal impact of the project can be best seen as the inclusion of data for the WHO Paediatric ARV working group; various members of PENTA LABNET participate in this working group and WHO is a partner in PENTA LABNET. Furthermore, the detailed immunological results from PENTA 11 support the basis under which circumstances treatment interruption in children may be safe, as well as important differences in immunological responses between children and adults.

The work in WP1 on physiologically-based recommendations for dose selection in children has a much wider impact than for HIV alone. Based on these models, pharmacologists from pharmaceutical companies may have better evidence for selecting paediatric doses as part of their PIPs. In this way, PENTA LABNET is also a good example of private-public partnerships.

1.7 Reference to the project public website and logo

Figure 1: PENTA LABNET Logo

Public WEB site URL: http://www.pentatrials.org/labnet.htm