International AIDS Society – Industry Liaison Forum

MAPPING GAPS IN CLINICAL RESEARCH IN RESOURCE-LIMITED SETTINGS
FOCUS ON PAEDIATRIC TREATMENT

8 February 2009, Montreal

SUMMARY MEETING REPORT

Introduction to ILF – Why focus on women and children?
ILF Co-Chairs Pedro Cahn and Elly Katabira

ILF Co-Chairs Drs. Pedro Cahn and Elly Katabira welcomed meeting participants and provided regrets from Michael Rabbow, the ILF Industry Co-Chair, who was unable to attend.

Elly Katabira outlined the background on ILF and its role within IAS of fostering greater support and involvement of the pharmaceutical industry in clinical research in low and middle-income countries, noting that ILF was increasingly involved in regional partnerships and meetings as well as IAS-convened conferences. He referenced the focus of ILF in its new strategic plan (2008 – 2011) on clinical research that addresses women and children, to be discussed in greater detail later in this meeting.

Paediatric HIV Research: Status, priorities and ethical considerations
Dr. Nigel Rollins, Child and Adolescent Health and Development, WHO

Nigel Rollins presented current HIV epidemiology and antiretroviral therapy (ART) coverage levels for paediatrics. He noted that ART coverage (including PMTCT), has increased substantially over the past few years but is still highly variable within countries and remains a significant problem. Clinical outcomes for children reported by several ART programmes are good, but most are still starting ART late in disease progression, with most children being started on ART between four and nine years of age. As a result, there is high morbidity and mortality especially in the first six to twelve months of treatment. He emphasized that early identification and delivery of appropriate paediatric treatment (including appropriate formulations) is key to increasing coverage and reducing morbidity and mortality.

He noted that tuberculosis (TB) is a major driver of morbidity and mortality, with one-fifth of all TB cases occurring in children and young people. TB, HIV and malnutrition are endemic in sub-Saharan Africa and TB is the most common cause of illness and death in people with HIV in Africa. Children living with HIV are up to 20 times more likely to develop TB than HIV negative children; however, data on children co-infected with TB and HIV are limited and the burden of HIV among confirmed clinical cases of TB in children ranges from 11-70%.

Research priorities for both adults and paediatrics regarding TB and HIV include:

- Understanding the burden of TB
- Better TB diagnostics that do not rely on sputum samples
- Clear guidance on optimal regimens and timing for treatment of TB and multi-drug resistant TB (MDR TB) in combination with ART
- Testing a TB vaccine and ensuring its safety/tolerability in children
- Development of a new, more effective TB vaccine

He noted that significant progress has been made in preventing mother-to-child transmission (PMTCT), with 81% of 109 countries reporting to UNICEF and WHO at the end of 2007 that they are implementing PMTCT programmes. The coverage of pregnant women receiving antiretroviral drugs for PMTCT increased from 10% in 2004 to 33% in 2007. While this is an improvement it is still wholly unsatisfactory. However, he added that the availability of PMTCT services varies tremendously between and within countries.

As of 2007, of all HIV positive pregnant women receiving antiretroviral prophylaxis for PMTCT, nearly 50% were still receiving only single-dose nevirapine. This approach is much less efficacious compared to the WHO-recommended course of antepartrum zidovudine and an intra and post-

partum regimen of zidovudine/3TC and single dose nevirapine to the pregnant woman and the newborn infant (or as part of a standard ART regimen for treatment-eligible pregnant women).

He also highlighted the need to focus on diagnostics (the proportion of pregnant women who received an HIV test increased from 10% in 2004 to 18% in 2007); implementation research and system delivery issues; (including testing and access to prevention interventions). He cautioned that clinical research results have not generally resulted in interventions that have been broadly scaled up (efficacy does not necessarily translate into effectiveness).

With increasing efficacy of interventions to reduce peripartum transmissions, breastfeeding now accounts for one third to one half of all HIV transmission from mothers to their infants. WHO recommends that HIV-infected women breastfeed their infants exclusively for the first six months of life, unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants.

Rollins presented data from four observational studies: Dream Plus (Mozambique), Mitra Plus (Tanzania), Amata (Rwanda), and the Kisumu Breastfeeding Study (Kenya), all of which demonstrated that very low transmission rates can be achieved in breastfeeding women using maternal triple ARV prophylaxis/therapy while retaining the benefits of breastfeeding.

He also referenced the SWEN study (Ethiopia, India and Uganda) and the PEPI-Malawi study, both of which demonstrated that infant-only extended ARV regimens are practical and effective in reducing HIV transmission and improving HIV-free survival in settings where breastfeeding is common.

He noted that implementation research was not well-understood or funded, and emphasized its importance in answering key health care delivery questions using a multidisciplinary approach and a variety of skills sets and perspectives.

Rollins also noted the unique ethical issues in paediatric HIV research, including balancing the interests of the mother and infant, consent issues, sexual and reproductive health rights of HIV positive adolescents, and the impact on and the responsibility of research centres in addressing local quality of care issues rather than setting up parallel health care delivery structures. He also raised the question of whether it was ethical to research models of paediatric care that could not feasibly be scaled up in developing countries.

Rollins ended his presentation by outlining a number of paediatric and maternal clinical research priorities, including:

- How best to early identify infected children
- How to effectively monitor disease progression in this population (and in resource-poor facilities)
- Examining the feasibility of nurse-led ART initiation and management
- Maternal ARV regimens for prophylaxis (including evaluating the optimal duration and regimen for prophylaxis, the impact of starting and stopping ARV prophylaxis on maternal health and future treatment options and feasibility and cost issues)
- Extended infant ARV prophylaxis (including optimal duration and safety of extended nevirapine or other ARVs, resistance and its impact on prophylaxis and future treatment options for infants, and evaluating in what circumstances would infant prophylaxis be preferable to maternal prophylaxis)
- Infant feeding (including determining the circumstances in which to recommend a woman stop breastfeeding at 6 months and the impact of not breastfeeding on subsequent infant growth and development)

ART in Children: Clinical and Pharmacological Aspects
Dr. Mark Cotton, KID-CRU, Tygerberg Children's Hospital, South Africa

Mark Cotton started his presentation by noting that the most important questions that need to be answered in paediatric research are when to start ART, what regimen to start with and whether treatment can be interrupted.

He outlined the impact of HIV infection on infant morbidity and mortality and presented data from the Children with HIV Early Antiretroviral Therapy (CHER) trial, which is assessing whether early diagnosis and either deferred, short course (to one year of age) or long course (to the second year of age) ART will delay subsequent disease progression and the need for long-term, continuous ART. The study has already demonstrated a reduction in early infant mortality among those receiving early ART initiation by more than 75%.

Presentation highlights included:

- The need for better treatment and care options for infants in community settings
- New data on infant mortality in South Africa reveals the highest risk among infants are between 2 -3 months of age
- Need to review WHO guidance to see if a more nuanced approach and earlier initiation is required for updated normative agency guidance

Mark briefly outlined studies that are assessing different approaches to paediatric diagnosis and treatment; the Paediatric Randomised to Early versus Deferred Antiretroviral Initiation (the PREDICT study) in Cambodia and Thailand (estimated to complete in late 2011), PENTA 11, the first randomised trial of planned treatment interruptions (PTIs) in HIV-infected children, BANA 2, a randomised trial of continuous versus intermittent ART in HIV-infected infants and children in Botswana, and PENPACT1 on combination of ARV regimens and treatment switching strategies in HIV-infected, ARV naïve children, IMPAACT P1060, a randomised trial comparing the responses to initiation of NNRTI-based versus PI-based ART in HIV-infected infants with no prior experience of single dose nevirapine for PMTCT.

He noted several programmatic issues related to paediatric treatment, including the need for the majority of infants to be placed on ART within their first year of life and how current diagnostic strategies in low income countries limits the ability of health care workers to diagnose and provide appropriate care to HIV-positive infants. WHO currently recommends a diagnostic PCR between 4 – 6 weeks of age, although in South Africa this is rigidly interpreted as 6 weeks, which coincides with infant immunization. He pointed out that this might be too late and suggested stratifying infants using clinical algorithms, although he cautioned that currently little is known about ARV pharmacokinetics in the first 3 months of life. There are a number of studies looking at the pharmacokinetics of new and re-formulated drugs, e.g. raltegravir, vicirviroc, TMC 125, paediatric alluvia, and others.

Cotton also raised the need of improving the transport, storage, as well as administration of paediatric formulation ARVs.

He noted that a major report from WHO on dosage forms of medicine for children was released in December 2008, which emphasized convenient administration of ART for both health care workers and paediatrics (including the need to make medicines more palatable), transportability and stability in a variety of climates.

Cotton summarized that both first and second-line paediatric regimens could be improved (for example, thymidine-based Nucleoside reverse transcriptase inhibitor is a key component in both first and second-line ARV regimens for South African infants), that clinicians needed better knowledge about the best ARV dosing strategies for children over a year of age, a better understanding of ARV toxicity in children, the need for a paradigm shift with regard to PMTCT and accelerated efforts on improving paediatric drug formulations.

Participant Discussion

A number of speakers noted the significant palatability problems associated with some important paediatric drugs, such as ritonavir and ritonavir/lopinavir. It was noted that the substantial costs associated with developing paediatric formulations affected their commercial viability for industry, with companies primarily producing paediatric formulations as a result of social responsibility rather than anticipated profits.

Participants also reinforced calls for operations/implementation research and on the need for pilot studies (e.g., cluster studies modeling, particularly those focusing on different strategies/approaches) to address knowledge gaps in paediatric care and treatment.

One strategy suggested was to treat infants born to HIV-positive women on the assumption that tests will come back positive, thereby optimizing treatment benefits and reducing early infant morbidity and mortality.

Participants emphasized that industry is good at assessing the hurdles in getting a drug to market in the developed world and could look at which of those processes can be adapted for the developing world.

The question was raised of how many children need paediatric formulations; a substantial proportion can take adult formulations. Some cost/benefit analysis is required and one of the questions raised is whether industry is best-equipped to do this and whether every company would need to establish a centralized pharmacokinetics group to develop each molecule for adaptation to paediatric populations.

Shirin Heidari introduced the following presentation by summarizing the consultation process and development of the ILF Strategic Plan: 2008 – 11, which was approved at the ILF Advisory Group meeting held in conjunction with the XVII International AIDS Conference (AIDS 2008) in August 2008. The plan includes a focus on addressing the research needs of women and children. ILF-sponsored meetings on this theme were held in conjunction with the Conference on Retroviruses and Opportunistic Infections (CROI) in 2008 (on defining a research agenda for women in resource-poor settings) and at AIDS 2008. A substantial piece of work in addressing this objective is the following proposed mapping exercise.

Map the Gap: Research Gaps in HIV Treatment and Prevention for Women and Children
Rodney Kort, Consultant

Rodney Kort began by providing a brief overview of HIV epidemiology, ART coverage and some outstanding research questions (such as potential sex difference in pharmacokinetics) related to women and children. He noted that the purpose of the mapping exercise was to establish an overview of the HIV clinical research (biomedical prevention and treatment) landscape related to women and children, including recommendations for priority research investments. The mapping exercise will include the following phases:

1. Confirm the scope, partners and process for the exercise in consultation with the ILF Advisory group and relevant stakeholders (including senior investigators).
2. Conduct an environmental scan of research on women and children, including a review of grey and scientific literature, a survey of stakeholders involved in research on women and children and key informant interviews with organizations advocating for, funding and implementing research on women and children.
3. Prepare a draft report summarizing the key findings from the environmental scan, including draft recommendations on priority research questions
4. Host a multi-stakeholder consultation in conjunction with the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2009) on the draft recommendations from the report
5. Finalize the report and issue a consensus statement with partners (e.g., WHO, UNAIDS, UNICEF, International Centre for Research on Women, EGPAF) on priority research and required investments in research on women and children.

An ILF Expert Reference Group will be established to provide strategic direction and advice on the project, which is scheduled for completion in August 2009.

Perspectives from Stakeholder Groups : Roundtable discussion

Meeting participants supported the project as outline and encouraged establishing partnerships and buy-in from other stakeholders early on to help asses who has already done work in this area and using that to shape process, outputs and outcomes, including recommendations and a plan of action in moving forward on priority research questions

Participants also agreed the scope should focus on clinical research but also address delivery and programmatic issues (operations research) as sub-component given their relevance in the developing world. Other issues that should be included in the mapping exercise are:

1. Research required to develop paediatric formulations (including generic manufacturers who deliver many ARVs in low and middle-income countries)
2. Challenges and barriers in R&D and getting ARVs to market
3. Best practices in private/public partnerships and how they could be leveraged to help guide drug development and distribution
4. The pharmacokinetic levels that result in good dosing recommendations

Elly Katabira thanked participants for their input and adjourned the meeting.