MEETING REPORT

International AIDS Society – Industry Liaison Forum

Pharmacology of ARVs: How HIV-1 infection differs in children and women
5 March 2012
CROI 2012
Seattle, USA
BACKGROUND

In 2010, the International AIDS Society-Industry Liaison Forum (IAS-ILF), jointly with 15 other organizations (including WHO, UNAIDS, pharmaceutical companies, non-governmental organizations and community groups), released a consensus statement, *Asking the Right Questions: Advancing an HIV Research Agenda for Women and Children*, which outlined 20 recommendations to advance HIV research for women and children. Six of those recommendations call for more investment in clinical research related to the unique needs of paediatric treatment of HIV-1 infection. In addition, there is a set of recommendations on accelerating clinical research for women and girls, including the need to better understand potential differences in pharmacokinetics and pharmacodynamics of antiretroviral (ARV) drugs in these populations.

As part of the continuing effort to promote HIV research related to children and women, the IAS-ILF organized an affiliated event in conjunction with the Conference on Retroviruses and Opportunistic Infections (CROI) 2012 in Seattle, Washington, USA. The objective of this full-day meeting was to highlight the current evidence on ARV pharmacology in both paediatric populations and women. The morning session was devoted to neonates, children, adolescents, and paediatric populations with special needs, including with concomitant conditions such as TB, malaria and malnourishment. The afternoon session focused on women and girls, with emphasis on the unique ARV pharmacological considerations for adolescent girls, ARV interactions with hormonal contraception, and aging. Both sessions had a series of presentations by experts, followed by a roundtable discussion to identify the key challenges in future ARV pharmacological research and the clinical management of these populations.

ARV PHARMACOLOGY IN CHILDREN

The morning session was co-chaired by Chewe Luo (UNICEF) and Shaffiq Essajee (Clinton Health Access Initiative), who provided opening remarks. Luo presented a background of the IAS-ILF’s mission and efforts to accelerate HIV clinical research in children. After addressing the knowledge gaps in ARV pharmacology for infants and older children, Essajee introduced the first speaker of the session.

Edmund Capparelli

*Overview of pharmacology in paediatric populations: from neonates to adolescents*

Edmund Capparelli provided a foundation of ARV pharmacology in children, with a focus on human development and the spectrum of infancy to adolescence. He highlighted paediatric developmental changes that impact clinical pharmacology and disease progression, including fluctuations in pH and in the gastrointestinal tract, coupled with modifications in body composition, all which are experienced in the early years of a child’s life. Regarding important changes in enzymatic activity, Capparelli noted that some gene expression is low in infancy and then gradually rises with age. He also emphasized that our knowledge of physiological changes can dictate the dosing, and commented that understanding metabolic pathways in children (as with renal function) is
particularly important. Notably, renal function in children is best characterized, while drug metabolism and absorption are the areas where critical gaps in knowledge remain.

From a practical standpoint, the development of a single fixed-dose combination (FDC) ratio across the full paediatric age spectrum, which would achieve exposure levels that are comparable to those of adults, is improbable. Enzymatic activity varies considerably from birth to adolescence (Figure 1), and consequently, paediatric doses needed to attain adult exposure are age dependent. Capparelli described the well-characterized developmental changes in clearance for zidovudine (ZDV), noting the tremendous between-subject variability, and presented data for neonatal ZDV clearance showing lower levels of clearance in premature infants. Understanding clearance changes has important implications for determining safe dosages.

![Figure 1](image.png)

**Figure 1.** Human enzymatic activity from birth

In the context of ARV pharmacokinetic/pharmacodynamic (PK/PD) for adolescents, the US Food and Drug Administration (FDA) categorizes anyone older than 16 years as an adult. However, adolescents are recognized for having better renal and hepatic function than older adults, and optimal physiology in adults is considered to be around age 20.

Capparelli proceeded to present PK data from two paediatric cohorts (Cohort 1, infants aged 14 days to six weeks; Cohort 2, infants aged six weeks to six months) on lopinavir (LPV) (dose 300mg/m²). In Cohort 1, with younger infants, median LPV concentrations were notably lower across a 12-hour period upon dose administration (Figure 2) than older infants in Cohort 2. The authors of this study indicated that, given low LPV exposure in new-borns, a higher dose for younger infants should be considered.

In terms of estimating the dose for patients, empiric data indicates that body surface area correlates better than weight for drug elimination. Notably, drug half-life in infants is shorter than adults. Capparelli pointed out that some additional factors (e.g., genotype, formulation) may also contribute to the ARV PK variability in paediatric populations.
Pharmacodynamics is also a critical aspect of pharmacology in children, with the risk/benefit of infant therapy being different, as demonstrated by the CHER study. In this study, HIV-infected infants aged six to 12 weeks (median 7.4 weeks) were randomized to either deferred treatment or immediate treatment (ZDV, 3TC, LPV/r). The immediate treatment arm had a lower probability of death or CDC stage B or C events.

Capparelli presented data showing variability in ARV breast milk/plasma ratios for zidovudine (ZDV), lamivudine (3TC), and nevirapine (NVP), with NVP showing higher levels in breast milk than plasma, as compared with ZDV and 3TC. Analysis of drug levels in dried blood spots also showed higher NVP concentrations in breast milk, while ZDV could not be detected in DBS.

In closing, Capparelli reiterated the point that growth and development in the earlier years has a significant impact on how drugs are metabolized and eliminated. He pointed towards the greatest knowledge gap in understanding how developmental changes impact ARV PD and PK, and how toxicity and disease progression can ultimately impact paediatric care.

Philippa Musoke

*Antiretroviral pharmacology in children: how malnutrition impacts clinical management*

Philippa Musoke prefaced her talk by highlighting how there are varying degrees of malnutrition in children, suffering from both stunting and wasting, in resource-limited settings. Globally, an estimated 30-50% of children with severe acute malnutrition (SAM) are HIV infected. Non-oedematous malnutrition is more prevalent in HIV-infected children, and mortality in children with SAM is very high. In a study with 220 hospitalized Ugandan children, mortality was estimated at 24%, with 70% of the deaths occurring in the first week of hospitalization. In another study of 454 children with SAM in Malawi, overall mortality was estimated at 14.8% (35.45% in HIV-infected vs. 10.4% in uninfected children). The highest mortality was observed in those younger than 24 months of age.

1 SAM is defined as: weight-for-height z score < - 3SD expected for age/mid upper arm circumference < 11.5 cm/weight-for-age z score < -3 SD = wasting/height-for-age z score < -3 SD = stunting
Musoke also explained that the majority of children starting ART in Africa are older, with lower CD4 percentages, and severely wasted and stunted. Management of malnutrition recommended by World Health Organization (WHO) involves starting ART after nutritional stabilization. This typically involves the use of high-energy F75 milk (fortified with vitamins), and the administration of antibiotics. Following the rehabilitation phase, there is a switch to F100 milk (100kcal/100mls).

Musoke presented weight-for-age z-scores (WAZ) and height-for-age z-scores (HAZ) data for children on ART noting that mean scores for all children (irrespective of starting WAZ/HAZ band) increased over time (Figure 3). However, children in lower WAZ groups tended to experience greater immunological/virologic failure. In another comparative study examining ART responses between subjects in UK/Ireland and Uganda (Figure 4), there were smaller gains in weight among Ugandan children the older they started ART whereas there was little variation in weight response after seven years of age in the UK/Ireland group.

![Figure 3. Mean WAZ (left) and HAZ (right) scores from baseline to 48 weeks in the VS/IS treatment outcome group according to age category (Musoke et al, BMC Pediatrics 2010 10:56)](image)

In presenting PK data of ARV in moderate and severe malnourished children, Musoke underscored the fact that all PK parameters may be affected by malnutrition, including drug absorption, protein binding or metabolism. In severe malnutrition, there is reported reduced drug absorption (e.g., villous atrophy of the intestinal lining, along with reduce gastric acidity) and lower levels of serum albumin, which is associated with reduced binding of some drugs. Importantly, diarrhoea and micronutrient deficiency impact absorption. Musoke noted that some evidence suggests that NVP levels are rather age-dependent than on the degree of malnutrition in a comparison of normal vs. mild-moderate malnourished children. Another study in Malawi and Zambia reported lower NVP plasma concentrations in stunted children, while wasted children were observed to have higher NVP levels.
Figure 4. Effect of age at ART initiation on viral load, CD4, height and weight at six months

Musoke highlighted the need to examine the effect of SAM on the PK of ARV drugs, coupled with determining when to start ART in children with SAM. Furthermore, the question of whether nutritional supplementation during ART initiation improves overall outcome remains unanswered.

Musoke concluded by listing a set of research priorities identified in a WHO expert meeting (1-3 February 2012) to update the WHO recommendations on the management of children with severe malnutrition. They include: (a) establishing PK characteristics of HIV-infected children starting on ART; (b) establishing PK of other drugs, including INH; (c) effectiveness (survival and complications) of early vs. late initiation of ART in SAM children with HIV; (d) establishing the relationship between ART regimens in HIV-infected children on ART e.g. dosing and development of early complications, such as acute malnutrition and oedema or later metabolic complications, such as immune reconstitution syndrome (IRIS); (e) determining the most effective therapeutic feeding approach for HIV-infected children with SAM with persistent diarrhoea; and (f) determining if the basic physiological abnormalities of HIV-infected children with SAM, with or without oedema are the same as for children with SAM without HIV, and describing significant differences.

Sunil Parikh
*Malaria & HIV: treatment considerations in co-infected children*

Sunil Parikh highlighted that malaria and HIV are overlapping epidemics, with a global burden of approximately 0.5 billion malaria cases (with an estimated 863,000 deaths/year). Children younger than five years and pregnant women are at highest risk. Parikh noted how both diseases interact bi-
directionally, although more data currently exists on the impact of HIV on malaria, while less is known about the impact of malaria on HIV. HIV is associated with increasing prevalence of clinical malaria in both children and adults, given the state of immunosuppression. Furthermore, HIV can increase the risk of placental malaria, high-density parasitemia, impaired acquisition of maternal immunity, adverse fetal outcomes, and higher placental viral load. Conversely, malaria is associated with a 0.67 log₁₀ copies/mL increase in plasma viral load, and decreases in viral load following treatment for malaria (meta-analysis by Barnabas RV et al, AIDS 2011).

For HIV/malaria co-infected patients, Parikh noted that one has to consider the direct antimalarial effects of ARVs, as well as the antimalarial-ARV interactions. Artemisinin-combination therapies (ACTs) are the most commonly prescribed antimalarial regimens, although there are other drugs used for prophylaxis and severe disease. Monotherapies are less prescribed as a result of the emergence of resistant malaria strains. ACTs combine a short-acting artemisinin derivative used in combination with a long-acting partner drug. Parikh commented on the urgent need for PK studies of ACTs in children and pregnant women living with HIV. Additional issues to consider are the impacts of co-administration of antimalarials and antiretrovirals on drug toxicity and efficacy.

Parikh described some of the most widely adopted treatments for malaria, and commented on the increasing use of LPV/r-based treatment (and the widely prescribed non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens of efavirenz or nevirapine) in co-endemic regions of HIV and malaria. Interestingly, PIs have an in vitro inhibitory effect on malaria parasites at clinically relevant concentrations (Parikh S, et al. AAC 2005). Notably, HIV and malaria both have aspartic proteases. Parikh also noted that more recently PIs and lumefantrine (LR) were found to show in vitro synergy (also CQ and mefloquine).

Artemether-lumefantrine (AL) is currently the most widely adopted regimen in children. In a study of healthy volunteers (Figure 5), a two to three fold increase in lumefantrine (red line with LPV/r) was observed when used in combination with LPV/r. Conversely, data is emerging that levels of artemisinin derivatives and lumefantrine are reduced to varying degrees in the presence of NNRTI. The second most commonly adopted ACT, artesunate-amodiaquine was also shown to lead to hepatotoxicity when co-administered with efavirenz.

![Figure 5. Effect of LPV/r on lumefantrine levels.](image)
In order to determine whether ART-AL PK interactions are clinically relevant, Parikh underscored the need to conduct intensive and population PK sampling in HIV-infected individuals during malaria episodes. His team has developed small-volume sampling techniques to get samples at the same time as obtaining finger prick blood for malaria. Parikh also cited an abstract being presented at CROI 2012 from a paediatric trial in Tororo, Uganda investigating whether LPV/r or NNRTI-based regimens had an impact on malaria incidence. Intention-to-treat analysis indicated a 41% reduction in malaria associated with LPV/r-based ART. Parikh and colleagues are conducting PK studies of ACTs and ARVs in the context of this trial, and a similar trial occurring in pregnant women.

Many ACTs appear to be under dosed in HIV-infected children, and there is PK evidence showing lower LR area under the curve (AUC) levels in children when compared with adults (Figure 6). LR levels are also reduced in younger children (six months to two years old) when compared with older children (five to 13 years old). Safety and efficacy of antimalarial therapy can also be affected by HIV status. In a study of children receiving artesunate/amodiaquine for malaria, those receiving ARVs had the highest rates of neutropenia. Furthermore, higher rates of antimalarial treatment failure in adults have been reported, but not in children, although sufficient studies in the era of ACTs are lacking.

![Figure 6. Lumefantrine levels in malaria-infected children and healthy adults](image)

Parikh concluded his presentation by addressing the role of co-trimoxazole prophylaxis in HIV-infected persons in reducing the burden of malaria. Currently, TMP-SMX is recommended in most HIV-infected individuals in resource-poor settings, while sulfadoxine-pyrimethamine (SP) is used as intermittent preventive treatment for malaria in pregnancy. In one Ugandan study, the combination of TMP-SMX and bed nets was associated with a 97% reduction in the incidence of malaria in HIV-infected children. However, Parikh noted that there is concern over cross-resistance for both TS and SP, and that the prophylactic efficacy/toxicity of antimalarials may be altered in the presence of ARVs. Parikh’s emphasized that further studies are needed to evaluate other ACT regimens in the context of ARV treatment, as data have emerged suggesting that both the efficacy and toxicity of ACTs may be impacted by interactions with ARVs. The take home message was that more studies are warranted in the era of ACTs; further studies of the impact of TS and other potential prophylactic malaria regimens in the setting of HIV are needed.
Helen McIlreron

Treating HIV in children with tuberculosis

TB is a major cause of mortality in children younger than five years in sub-Saharan Africa, with young children being particularly susceptible to TB. In high-burden settings, up to 25% of children with untreated HIV infection develop TB annually. Helen McIlreron noted that introducing ARVs during TB infection dramatically increases survival, but underscored the challenges that remain in the clinical management of children, including large pill burdens, complex dosing schedules, overlapping drug toxicities, drug-drug interactions, and development of immune reconstitution syndrome (IRIS).

Rifampicin is the cornerstone of TB treatment, and is administered for six months. However, it is a potent inducer of multiple enzymes and transporters, namely CYP3A4, 2B6, UGT and P-glycoprotein, and consequently, it results in reduced concentrations of key ARVs. Furthermore, the accelerated production of toxic intermediates as a result of induction may contribute to increased toxicity.

For children younger than three years WHO currently recommends two NRTIs with NVP or super boosted LPV/r (Table 1). Notably, for children younger than two years with prior ARV exposure triple nucleoside reverse transcriptase inhibitor is recommended. Due to questions and concerns of inferior efficacy of triple NNRTI regimen and widespread use of NNRTIs both for ART and prevention of mother to child transmission, super-boosted LPV is used in some programmes. WHO advocates this approach only if the child with TB is already on a protease inhibitor (PI)-based regimen, while efavirenz (EFV)-based ART is preferred in children older than three years.

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<th>ART</th>
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<tr>
<td>3NRTIs&lt;sub&gt;1&lt;/sub&gt;</td>
<td>RI&lt;br&gt;AMPIN&lt;br&gt;Isoniazid&lt;br&gt;Pyrazinamide&lt;br&gt;Ethambutol&lt;br&gt;Co-trimoxazole</td>
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<td>Nevirapine + 2NRTIs&lt;sub&gt;2&lt;/sub&gt; or 3NRTIs</td>
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<td>super-boosted PI (LPV/RTV&lt;sub&gt;0&lt;/sub&gt;=1:1)+2NRTIs</td>
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<sup>1</sup>ABC+3TC+AZT/d4T; <sup>2</sup>3TC+ABC/AZT/d4T

**Table 1.** WHO guidelines for children

NRTI-only regimens have the benefit of the absence of drug-drug interactions. However, McIlreron pointed out studies in adults showing that these regimens remain inferior when viral load is high, as is often the case in children initiating therapy. High rates of NRTI mutations and virologic failure have been reported in children. In addition, rifampicin has the potential to reduce ABC and ZDV concentrations. There is concern over the use of this regimen in children with TB that has not been evaluated. Triple nucleoside regimens might be more suitable in the subgroup of children started on an effective ART regimen and virologically suppressed before they present with TB.

McIlreron described the reality that for many children under three years of age, a NVP-based regimen is the only available treatment option. She commented that there is limited data describing
NVP concentrations in young children with TB, but highlighted a study of 21 Zambian children on TB treatment (median age of 1.6 years), where 50% had a trough concentration less than the recommended range. There is an urgent need to further evaluate efficacy of standard doses of NVP in children with TB, while the potential toxicity of an increased dose of NVP would need to be evaluated.

Although LPV/r based regimens are increasingly the preferred regimens in young children, the extensive interactions with Rifampicin remain problematic. Importantly, rifampicin reduces LPV concentrations by 75% when administered with LPV/r. In adults, doubling the standard dose of LPV/r or adding extra RTV to LPV/r overcomes the effect of rifampicin on LPV concentrations. In contrast, doubling the dose of LPV/r failed to achieve adequate LPV concentrations in 20 young children with TB (Figure 7).

McIlleron pointed out that it is unclear why the double-dose approach preserved LPV concentrations in adults but not in young children. She described how some population PK modelling suggests that TB treatment reduce the bioavailability of LPV/r oral solution in children, more than it reduced that of LPV/r tablets in the adults. Additional studies are needed to evaluate differences in absorption and intestinal metabolism of different formulations.

Rifabutin is a derivate of rifampicin that does not substantially affect PI concentrations. However, PIs, especially RTV, inhibit its metabolism, increasing concentrations of the parent drug and 25-O desacetyl RBN. In adults on LPV/r, a dose of 150mg three times per week has been recommended. However, PK of rifabutin has not been evaluated in children and there is not a suitable formulation.

An EFV-based regimen is preferred in children with TB older than three years. Presenting data of mid-dose-interval concentrations of EFV in 40 children with TB and 41 control children without TB, McIlleron noted that there was wide variability in concentrations between subjects, largely accounted for by genetic polymorphisms of CYP2B6. Although EFV concentrations are more variable.
during TB treatment in children as in adult studies, they are not different overall during TB treatment compared with after TB treatment or in controls.

In closing, McIlerson called for the design of adequately sized studies. On the TB side, there is heavy debate over the prospect of new drugs, and a potent regimen without substantial interactions with paediatric ART regimens would be an enormous advantage in high-burden settings. There is a need for suitable formulations, especially for children being currently prescribed with three ARVs and four anti-TB drugs. McIlerson also indicated that there is insufficient evidence to support treatment guidelines and studies evaluating PK, while safety and efficacy data are needed to evaluate current and alternative approaches.

**PANEL DISCUSSION**

*Panel moderator:*
Jintanat Ananworanich HIV-NAT, The Thai Red Cross AIDS Research Centre

*Panel participants:*
Shing Chang Drugs for Neglected Diseases *initiative* (DNDi)
Brian Kearney Gilead Sciences
Angela Nilius Abbott Laboratories
Jaideep Gogtay Cipla

Following the insightful presentations, Jintanat Ananworanich, a clinical trials physician and paediatrician, welcomed a panel of pharmacology experts. The panel consisted of representatives from three originator companies and DNDi, a non-profit research and development (R&D) organization focused on the development of treatments for neglected diseases.

**Shing Chang**, R&D director of DNDi, commented on the relatively few ARVs for paediatric populations compared with those for adults, and described DNDi’s public health approach to addressing the treatment needs of children living with HIV. Chang also described how for children, a full regimen should be considered rather than a single drug. Historically industry responds to treatment challenges by developing single drugs. Furthermore, he noted that the “paediatric segment is the last segment” that industry enters into, although this is not consistent with the “sense of urgency” within the paediatric HIV community. Currently, for children, there is only a single PI available in an oral solution, which he argued should be replaced with a sprinkle formulation. The challenge in a fixed-dose combination (FDC) is to allow for the flexibility to replace an individual component with a new drug once that is developed and approved. Chang also indicated that super-boosting should be accounted for in formulation development.

**Brian Kearney**, head of Clinical Pharmacology at Gilead Sciences, commented that his company has been developing a sprinkle to overcome the challenge of tenofovir’s unpalatable taste. Based on unfavourable patient feedback in several investigations, it decided to go back to lower dosage and smaller tablet strengths dosage form. Echoing sentiments by Chang, Kearney also underscored how it would be helpful within the paediatric community to prioritize R&D.
Angela Nilius from Abbott Laboratories described her company’s efforts to carefully examine a range of oral solutions for Kaletra, and indicated that the chemical nature of drugs presents huge technical challenges. In terms of developing alternative formulations, Abbott is currently working on a ritonavir sprinkle, but she stated that it is much more challenging than one assumes. Nilius also pointed that Abbott thinks about the end users, the needs of children, and the needs of caregivers in developing a suitable formulation.

Jaideep Gogtay from Cipla commented on the complexity of examining regimens of three individual ARVs, but voiced his optimism in developing child-appropriate and highly efficacious FDCs. He noted, however, that this pursuit would require patience, and addressed the urgent need to develop a sprinkle formulation (with data from a pilot study being presented at CROI 2012). However, he urged caution on whether sprinkle formulations will be acceptable by caregivers and children themselves, and formulation developers should exercise consideration on that front.

A matrix of challenges

Ananworanich noted the complex issues in R&D being faced by pharmacologists and formulation developers. Ed Capparelli pointed out that although technology and expertise exist, the larger question is whether new formulations and regimens can be used and adhered to in a given population. In agreement, Diana Gibb (MRC, UK) commented that one has to think around issues of how a drug developed for adults can ultimately be used in children. In addition, she suggested examining the PK in scored tablets, and encouraged WHO to “talk the same language” to industry.

In light of the data presented earlier by Ed Capparelli, Hedy Teppler (Merck) indicated that oral solutions may be more suitable for younger children where dosing is particularly important by weight. Ananworanich asked Kearney how Gilead has addressed the intricacies of PK/PD and drug toxicity, particularly for tenofovir. Kearney described how the safety profile of a drug evolves over time, and although agencies and jurisdictions have different perspectives, companies like Gilead make a serious effort to work with them.

Ananworanich noted how higher ARV exposures in HIV-infected patients have been documented in Thailand, indicating different PK/PD in patients with different ethnic background. Given that WHO and other organizations have different dosing recommendations in their treatment guidelines, she asked the panel why establishing appropriate drug dosing remains a challenge in paediatric populations (e.g., “is it because we don’t have enough studies?”). Nilius commented that regulatory agencies can draw different conclusions on paediatric dosing, even in the face of data that a company provides. Furthermore, she indicated that paediatric pharmacology is hampered with less data altogether, with “dose response data lagging behind”. Ananworanich also inquired whether we should advocate for more PK studies in different ethnic groups. Gogtay stated that it would be possible, and called for establishing a consensus between the FDA and WHO.

Essajee recommended on having WHO and FDA “work off the same template”. He described how the FDA assumes responsibilities of considering a generic dossier to determine how that matches with an originator for dosing that was approved. Essajee commented that in many cases, there are
no existing dosing formulas to follow, and ultimately, it remains very difficult to develop a sensible strategy. He indicated that WHO recognizes the problem, while the FDA is aware that clinicians are not using packaging instructions to dose, but are using dosing tables published by WHO and other entities. Notably, in an online survey on dosing of approximately 400 clinicians, an estimated 98% of respondents indicated that they do not look at a packaging insert, but rather use their national dosing guidelines (which are often replicated from WHO).

*Power of merging*

Gibb gave the example of merging data from different regions to allow for a better understanding of differences between ethnic/racial groups.

Essajee also proposed that guidelines should account for differences, but recommendations should be delivered in a way in which a community health worker can read them and safely deliver treatment to a patient. Ananworanich indicated that for any given drug, the PK difference may not have clinical impact, but determining that requires the collection of quality data. Gibb emphasized the need to examine the practical issues and to ask children and caregivers what they desire. She provided examples of where certain caregivers prefer tablets to carrying liquids, while a grandmother without glasses is unable to use a syringe to draw the liquid dose.

Kearney, when asked whose responsibility it is to develop drugs that are appropriate for co-conditions, indicated that as drug developers, they do not account for the malnourished child in a PK research protocol. However, Gilead has worked actively in public-private collaborations to ascertain the PK correctly. In P1092, Musoke also indicated how companies are providing drugs for the study to determine whether there is a PK difference to warrant a change in dose. Chang stated that one of the greatest challenges is TB-HIV co-infection, where there are multiple drug-drug interactions and a need to undertake proper studies.

In closing, there was recognition among speakers, panellists and other participants that practitioners, pharmacology experts and the community can inform companies about what is preferable and acceptable by caregivers and patients.

**ARV PHARMACOLOGY IN WOMEN**

The afternoon session was co-chaired by Shirin Heidari (IAS-ILF) and Prof Charles Boucher (Erasmus University Rotterdam). In opening up the session, Heidari highlighted much of the recent work by the IAS-ILF in mapping the clinical and operational research gaps in HIV-1 infection in girls and women. In addition, she raised the issue of women’s participation in clinical trials, and how they have been underrepresented historically in research. Boucher welcomed the first speaker of the afternoon, Prof Mark Mirochnick from Boston University Medical School.
Mark Mirochnick
*From puberty to pregnancy: ARV pharmacology in women*

Mark Mirochnick set the scene for the afternoon session by providing an overview of the existing data on ARV pharmacology for adolescent girls and pregnant women. He touched upon some recognized gender differences in ARV pharmacology\(^\text{15}\), stating how women have modestly higher plasma concentrations for saquinavir (SQV), ritonavir (RTV), EFV, NVP, enfuvirtide (INN) and LPV. Notably, some of these differences in PK may have clinical significance. Higher SQV concentrations in women have been associated with improved virologic responses, while higher RTV concentrations are associated with increased side effects. Furthermore, there have been reports of increased intracellular concentrations in women of carbovir triphosphate (CBV-TP) (after ABC administration), ZDV-TP and 3TC-TP\(^\text{16}\).

Mirochnick proceeded to describe the likely impact of adolescence on ARV pharmacology, and underscored how both PK and PD are impacted by adherence and behavioural issues. Mirochnick commented that adolescents could have differences in receptors and receptor activity from adults. Importantly, there may be PK/PD differences between newly diagnosed adolescents (through risk), versus those adolescents diagnosed at birth. Generally, there is some PK data for licensing purposes, but Mirochnick called for more in-depth studies in this population.

Developmental changes impact drug elimination, with a general trend of a peak in childhood to a drop in clearance. In terms of a potential gender difference in enzymatic activity, Mirochnick presented data on the changes in CYP1A2 (responsible for caffeine metabolism), which showcased an earlier (and more rapid) decrease during adolescence in females than males. PK data for abacavir from IMPAACT P1018 and P1052 indicate that clearance is higher at a younger age, and declines as children get older. Mirochnick noted the concern of overdosing in adolescents receiving ARV therapy, and commented that there is a paucity of data showing gender differences in ARV pharmacology in adolescents.

Pregnancy and adolescence are not mutually exclusive. Pregnancy itself is associated with a range of physiologic changes that can impact drug disposition, including macro changes in drug function, and changes at the molecular level that may alter bioavailability (e.g., protein binding decreases). Pregnancy-induced effects on the PK of SQV, RTV, LPV, ZDV, darunavir (DRV) and atazanavir (ATV) have been described. Mirochnick indicated that the PK parameters for a given drug depend on the enzymatic pathway being considered. Importantly, CYP34A for PIs is of greatest concern, while the 2B7 elimination pathway for ZDV is increased in pregnancy.

Data for ABC exposure during pregnancy\(^\text{17}\) (Figure 8) indicate (for a within-subjects comparison) no difference in ABC plasma concentrations during pregnancy and post-partum. However, these women had a slightly lower \(C_{\text{max}}\) and higher \(C_{\text{inh}}\) during pregnancy than post-partum.
Past studies of the PK of several protease inhibitors (including IMPAACT P1026s) during pregnancy have demonstrated reduced plasma drug exposure in pregnant women. Mirochnick presented data indicating that a higher LPV/r dose (533/133mg) provided LPV exposure during the third trimester similar to the median AUC in non-pregnant adults taking standard doses. Given this evidence, he commented that increasing PI doses in pregnancy cannot rest on the PK of ARVs in pregnancy (as we have significant data for this) since there is much less PD data. Mirochnick noted that drugs are first approved for non-pregnant adults, and then prescribed in pregnant women.

In closing, Mirochnick touched upon some considerations for inclusion of pregnant women in clinical trial design. Pre-clinical studies are necessary and critical prerequisite, followed by studies to determine the PK and safety for both pregnancy and the post-partum period (including protein binding studies). In reference to some innovative techniques, pharmacologists can explore the use of opportunistic design, population PK analysis, and stable isotopes for bioavailability studies. Lastly, Mirochnick noted that safety assessments require case control studies, meta-analyses and/or post-marketing surveillance.

Kathleen Squires

*Interactions of ARVs and hormonal contraceptives*

Kathleen Squires addressed the critical and contemporary topic of hormonal contraception (HC) and HIV-1 infection, underscoring the importance of HC in family planning. Squires commented that although preferred regimens for treatment in the US do not consider gender, they do highlight the concern of EFV use in women who are interested in getting pregnant. In raising the question of whether we should target certain regimens for use in men versus women, Squires described a recent FDA meta-analysis of ARV registration studies (43 randomized controlled trials for 16 ARV agents from 2000 to 2008) that demonstrated no statistically significant gender differences in week 48.
efficacy outcomes (HIV RNA<50 copies/mL at week 48) where 20% of the total 22,411 subjects were women.

Squires proceeded to describe some of the reported interactions between ARVs and HC. Notably, for oral agents, PIs and NNRTIs may increase or decrease levels of ethinyl estradiol, norethindrone and norgestimate, and could be associated with either contraceptive failure, or estrogen/progestin) adverse effects. In such a context, one may consider alternative or additional contraceptive method if used with interacting ARVs. Squires also noted that there is a paucity of data on the transdermal patch, vaginal ring and depot medroxyprogesterone acetate (DMPA), but there is evidence suggesting that the IUD is safe and effective.

In terms of HC and NNRTI interactions, there are reports on the use of EFV and NVP (Table 2). Squires highlighted the significant reduction in levonorgestrel and nonrelgestromin in women on EFV treatment, which would lead to failure of contraception.

In terms of HC and boosted PI interactions (Table 3), HC does not affect the PI itself. However, ritonavir inhibits CYP3A4, and surprisingly, instead of an increase, there are reports of a decrease in estrogen.

<table>
<thead>
<tr>
<th>Medication</th>
<th>NNRTI</th>
<th>Effect</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efavirenz</td>
<td>ethinyl estradiol ↔ levonorgestrel AUC ↓ 83% norelgestromin AUC ↓ 64%</td>
<td>Use alternative or additional methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.</td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
<td>Etravirine</td>
<td>ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect</td>
<td>No dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td>ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19% depomedroxyprogesterone acetate: no significant change</td>
<td>Use alternative or additional methods.</td>
</tr>
<tr>
<td></td>
<td>Levonorgestrel Efavirenz</td>
<td>levonorgestrel AUC ↓ 58%</td>
<td>Effectiveness of emergency postcoital contraception may be diminished.</td>
</tr>
</tbody>
</table>

**Table 2. HC and NNRTI interactions**

There has been a long-standing interest in understanding the potential impact of HC use on HIV risk. In terms of HIV acquisition, based on 20 prospective studies reviewed by a WHO consultation, the use of combination oral contraceptives was not associated with HIV acquisition in women. However, for progestin-only (DMPA), conflicting data suggests that there is either no risk or an elevated risk (with conflicting data indicating a range of 48-100% increase). Regarding transmission from HIV-1-infected women using HC to their uninfected male partners, a single observational study indicated a two to three fold increased risk with injectable contraception. The mechanism for this potential transmission risk has yet to be elucidated. A review of 10 observational studies saw no statistically significant association between HC use in HIV-infected women and disease progression (e.g., mortality, time to CD4 count <200 cells/m³).
Table 3. HC and RTV-boosted PI interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/r</td>
<td>↓ ethinyl estradiol ↑ norgestimate</td>
<td>Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%</td>
<td>Use alternative or additional method.</td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%</td>
<td>Use alternative or additional method.</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>ethinyl estradiol AUC ↓ 42% norethindrone AUC ↓ 17%</td>
<td>Use alternative or additional method.</td>
</tr>
<tr>
<td>Saquinavir/r</td>
<td>↓ ethinyl estradiol</td>
<td>Use alternative or additional method.</td>
</tr>
<tr>
<td>Tipranavir/r</td>
<td>ethinyl estradiol AUC ↓ 48% norethindrone: no significant change</td>
<td>Use alternative or additional method.</td>
</tr>
</tbody>
</table>

From a research standpoint, Squires underscored how the proportion of women participating in HIV clinical trials remains “modest” at best, despite comprising half the infected population globally. She noted that we have not observed a large rise in women’s participation, and stressed that we need data to inform treatment decisions. Squires also pointed to the higher discontinuation rates in women in many trials (with reasons for discontinuation being determined by study staff, not patients). She stated that the “real” reasons are not clear, as in the GRACE (Gender, Race, and Clinical Experience) study, where one in three of women dropped out of the study. Squires emphasized that gender differences between the adverse event (AE) profiles should be identified if they actually exist.

Women may differ from men in terms of the complications from highly active antiretroviral therapy (HAART). Women are at increased risk for a number of significant complications of HAART. Women receiving HAART may be more likely than men to develop hyperglycaemia, but less likely to experience hypertriglyceridemia. Nevertheless, increased breast size and abdominal girth may occur in women taking protease inhibitors. An increased risk exists for pancreatitis, fatal lactic acidosis and hepatic steatosis in pregnant women taking HAART, particularly regimens that include stavudine and didanosine. Amprenavir should also be avoided in pregnant women because its excipients include high levels of ethylene glycol. The use of protease inhibitors has been associated with decreased bone mineral density in women with HIV infection. Women being treated with nevirapine are at increased risk for severe skin rash relative to men receiving this drug.

There is also concern over lactic acidosis in women infected with HIV. Although a rare complication of prolonged usage of NRTIs, the majority of 60 reports by the late 1990s were in women (83%). Notably, 85% of the fatal cases (n=20) were in women. In an African study, 15 of 31 women who had lactate levels measured reported an AE, while 20% had severe hyperlactatemia (vs. 0% among men with a similar AE profile). This is one of the more clear associations of a gender difference in ARV-related complications.

Squires presented some final thoughts on PK and toxicity in HIV-infected women. She commented on the need to examine the association between PK differences and toxicity rates for newly approved and emerging agents. In more recent studies, such as CASTLE and ARTEMIS, reporting for
AEs has been low. However, Squires cautioned that larger studies will be needed to detect any real differences that may exist. One notable exception has been the GRACE study, which was properly powered to detect differences between men and women (67% of subjects were women). In closing, she noted that few studies have really demonstrated that higher drug levels are the explanation for the higher rates of discontinuation from some ART regimens.

Kristine Patterson  
*Women aging with HIV*

Kristine Patterson provided the closing talk by describing the emerging area of aging in HIV-infected women. She aimed to cover the extent of what we do not know in this area, despite more than 30 years of research. Patterson pointed to the complexity and sophistication of women’s biology, and commented that we need to understand the interface of HIV and naturally occurring hormonal fluctuations in females (from adolescence to menopause, and also depending on the current phase of their menstrual cycles). To date, the vast majority of HIV research efforts and funding has focused on women of childbearing potential.

Patterson commented that in the course of the next five to 10 years, an estimated 30% of new HIV infections in the US will be in those aged 50 years or older. Furthermore, she noted the need to better understand the physiological changes that occur in aging, since the loss of oestrogen may be associated with an increased risk in susceptibility. Patterson also indicated that we do not have much data to support this hypothesis.

According to two treatment-naive trials (ACTG 5095 and A5142), where menopausal status was clearly defined, no differences in immunologic or virologic responses were reported by age. Nonetheless, Patterson commented that studies from the early HAART era suggest that the degree and speed of immune recovery is likely reduced in older persons (although results have been mixed as some studies did not control for ART regimens). Other studies have reported that despite higher rates of virologic suppression, older individuals had an increased risk of death and new opportunistic infections compared with younger persons. Patterson clarified that most of these studies did not include enough mature women to differentiate sex outcomes. Cohort collaborations, such as the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), are critical in understanding the gender and age effects on HIV disease progression and opportunistic infections.

Potential differences in tolerability, discontinuation rates, AEs and complications have yet to be characterized in HIV-infected older women. Importantly, while ART has been understudied in older women, inflammation and immune senescence has not been studied at all. One area that has been examined is bone mineral density. Patterson described recent data demonstrating accelerated osteoporosis in women treated with tenofovir (compared with ART-naive women), and hypothesized that the driver is a PK complication of the drug. Based on data presented at last year’s CROI, Patterson reported two-fold higher plasma trough concentrations for tenofovir in post-menopausal women when compared with pre-menopausal women. Importantly, this accumulation may put older women at higher risk for AEs, such as renal toxicity.

Patterson expanded on the need to better understand cardiovascular disease (CVD), which is currently the leading killer of women in the USA. Questions remain about whether CVD is in fact
different in older HIV-infected women. Patterson made reference to the increased visceral adiposity in post-menopausal women, which has been linked with insulin resistance, dyslipidaemia and an increased risk of CVD. The underlying mechanisms are likely related to increased secretion of adipocytokines and other inflammatory markers, including t-PA and serum amyloid A. Reports from the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort suggest no association, but Patterson pointed out that the sample size of post-menopausal women and the number of CVD events was too small to make meaningful inferences. She also noted the need to better understand the type and timing of early replacement therapy in CVD outcome for older women.

In closing, Patterson reiterated the importance of the increasing prevalence of maturing HIV-infected women. She called for a better understanding of elements for prevention of HIV-1 infection in older women, including pathogenesis of acquisition, transmission biology, social determinants and stigma. For women who are already infected, treatment issues, including ART complications, PK/PD and inflammation, must be addressed in order to optimize care for this population. Ultimately, a treatment for post-menopausal women may necessitate different interventions from those for other HIV-1 infected groups.

**PANEL DISCUSSION**

*Panel moderator:*  
Catherine Hankins, UNAIDS

*Panel participants:*  
Heidi Nass, IAS-ILF  
Hedy Teppler, Merck  
Perry Mohammed, Janssen  
Nathalie Dang, ViiV Healthcare  
Richard Bertz, Bristol-Myers Squibb (BMS)

Following the insightful presentations, Catherine Hankins (UNAIDS), who serves on the IAS-ILF Advisory Group, welcomed a second panel of pharmacology experts from industry, along with a treatment activist from the community of people living with HIV. In her opening remarks, Hankins underscored the collective need to increase women’s inclusion in HIV clinical trials, and spoke about the issue of appreciating the differences between sex (a biological concept) and gender (a social construct).

**Nathalie Dang** is currently a Scientific Affairs Director at ViiV Healthcare, and the European Medical Lead for dolutegravir, an investigational integrase inhibitor currently being tested in a non-inferiority Phase III study called SPRING-2 (ING113086). Dang spoke of her interest in women’s HIV research and previous work in Japanese women.

**Richard Bertz** is a clinical pharmacologist and currently serves as Executive Director for Clinical Pharmacology & Pharmacometrics, Virology and Neurosciences at BMS.
Perry Mohammed, an HIV physician representing Janssen and a newly appointed member of the IAS-ILF Advisory Group, highlighted his company’s efforts to improve research related to special populations, particularly women. Janssen was an important player in the undertaking of GRACE, where woman’s participation reached approximately 50%.

Hedy Teppler, also a physician from Merck Clinical Research’s Infectious Diseases team, described her work on paediatric ARV development. She currently serves as the point person for raltegravir in children. In addition, she is actively involved in Phase III trials.

Heidi Nass, as a woman living with HIV, has been an active peer educator and community and treatment advocate in the US. Of note, she was recently invited to join the IAS-ILF Advisory Group. Nass commented on the complexity of issues affecting women, including stigma and discrimination, coupled with a lack of education, which contributes to women’s lack of retention in clinical research.

Enrolling women, prioritizing research

The topic of women’s enrolment in HIV clinical trial research was reinforced by panellists. In circumstances where the originally intended number of women is not enrolled, Bertz suggested that conducting a meta-analysis should be an option. He also spoke about the issue of companies being driven by what regulators require, and made a call for gender-based studies to be conducted. In response, Patterson stated that gender differences are not viewed as a priority by research networks, and underscored the fact that we still do not know what the optimal regimen is for treatment-naive women. Hankins also described how we are trying to create a new environment where we ask ourselves what is scientifically relevant.

Hankins commented on the dearth of information in pregnancy, particularly in the context of dosing. Bertz described how BMS has been conducting a smaller trial of atazanavir, and indicated how many companies have left much research to be undertaken by networks. He also spoke about the issue of better understanding treatment during pregnancy as more women living with HIV are electing to get pregnant. BMS conducted work in African pregnant women to determine side effects and establish a dose despite the study being underpowered to examine efficacy.

Hankins raised the issue of whether PK/PD studies can be conducted in pregnant women before a drug is licensed. Mark Mirochnick stated that this may not be unrealistic, referring to IMPAACT 1026S, which involved intensive PK analysis of approximately 400 pregnant women. Mirochnick also described previous work on a single dose of a gel in pregnant women, citing difficulty with an institutional review board (IRB) from one of the US universities until the CAPRISA results on efficacy were reported. He recommended that more education and communication with IRBs occur.

Hurdles everywhere

The challenges in undertaking research in women remain, particularly in light of the discontinuation of the oral tenofovir and tenofovir gel arms in VOICE following interim reviews of data. It was noted that final results from the discontinued arms of VOICE will be available next year.
Angela Kashuba (University of North Carolina, UNC) commented that some issues with inflammation may be associated with daily gel use. In reference to the struggle between regulators and IRBs, she shared her experience at UNC: they tried to do a study with raltegravir in pregnant women, where their IRB was supportive, but the FDA ethicist would not allow the study to proceed because it was outside standard clinical care (notably, they wanted to do some PK analyses).

In steering the discussion, Hankins raised the issue of conducting studies in adolescent females. Mirochnick commented on how they remain challenging to undertake, and noted that there are two different populations: one infected at birth, and one infected through sexual transmission in adolescence. The NIH’s Adolescent Trials Network (ATN) has done considerable work to get adolescent females into trials and care. Lynne Mofenson noted that the ATN is US-based, and suggested that its efforts be made global to have more impact (as the primary group of HIV-infected persons in the US is men who have sex with men).

In reference to the WHO consultation on HIV and hormonal contraception, Hankins indicated that the focus was not on the interaction between contraception and ARVs. In her talk, Squires said that most women who start ARVs initiate on NNRTIs, and commented that given pregnancy rates, many of them are not using condoms. Further, Hankins explained that the US Department of Health and Human Services (DHHS) guidelines on treatment have not been elevated to the international arena. Polly Clayden (i-Base) said that there was great uncertainty during the discussions at the WHO consultation. Notably, the HC options for African women are sobering. Kashuba, in a challenge to the pharmaceutical industry, argued that PD studies should measure ovulation. Bertz indicated that the challenge in trial design is to determine how many ovulatory cycles are needed to have an impact on efficacy (on which Kashuba noted they are working on a proof of concept study).

*AIDS 2012: an opportunity*

Annette Sohn suggested a follow up to this meeting at AIDS 2012, which can serve as a platform to fill in the already identified gaps. She also questioned whether this meeting would enable us to bring in funders and regulators. Squires also commented on how each year, the recurring theme is that there is a paucity of data, but no practical measures are being taken to move beyond general recommendations for “more research”. Investigator-initiated grants that could focus on women’s pharmacology are already in place in some companies.

Heidari commented that linking research agendas to funders and specific projects would be an attractive strategy; she also noted that prioritizing the specific needs of women in the context of research should be standard practice and not an extension where women are seen as some “special population”. AIDS 2012 will indeed be an opportunity to support the research movement to help address many of the outstanding issues and knowledge gaps related to girls and women.
### AGENDA

**Pharmacology of ARVs: How HIV-1 infection differs in children and women**

**Monday, 5 March, 2012 / 8:30 - 16:00**

CROI 2012 Affiliated Event, Red Lion Hotel Seattle - Emerald Room 2  
1415 5th Avenue, Seattle, Washington, USA

#### Objectives of the meeting:
1. To address the variability in ARV pharmacology for neonates, infants, children, and adolescents.
2. To address the unique ARV pharmacological needs of women during adolescence, pregnancy, and menopause with a particular role on the use of hormonal contraception and its impact on ARV PK/PD.

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>8:30-9:00</td>
<td>Registration and Breakfast</td>
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<tr>
<td>9:00-9:15</td>
<td>Welcoming remarks</td>
</tr>
<tr>
<td></td>
<td><strong>PART I – ARV pharmacology in paediatric populations</strong></td>
</tr>
<tr>
<td>9:15-9:30</td>
<td><strong>Overview of pharmacology in paediatric populations: from neonates to adolescents</strong></td>
</tr>
<tr>
<td>9:35-9:50</td>
<td><strong>ARV pharmacology in children: How malnourishment impacts clinical management</strong></td>
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<td>9:55-10:10</td>
<td><strong>Malaria &amp; ARV pharmacology in children</strong></td>
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<tr>
<td>10:15-10:30</td>
<td>Break</td>
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<td>10:30-10:45</td>
<td><strong>Tuberculosis &amp; ARV pharmacology in children</strong></td>
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<tr>
<td>10:50-12:00</td>
<td>Panel and roundtable discussion</td>
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<td></td>
<td>- Shing Chang (DNDi)</td>
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<td></td>
<td>- Brian Kearney (Gilead)</td>
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<td></td>
<td>- Angela Nilius (Abbott)</td>
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<td>- Jaideep Gogtay (Cipla)</td>
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<tr>
<td>12:00-13:00</td>
<td>Lunch</td>
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<tr>
<td>13:00-13:15</td>
<td>Introductory remarks</td>
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<tr>
<td>13:15-13:30</td>
<td><strong>From puberty to pregnancy: ARV pharmacological particularities in women</strong></td>
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<tr>
<td>13:35-13:50</td>
<td><strong>The interaction of ARVs and hormonal contraceptives</strong></td>
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<td>13:50-14:05</td>
<td>Break</td>
</tr>
<tr>
<td>14:05-14:20</td>
<td><strong>An aging population: Menopause, post-menopause, hormone replacement therapy and ARVs</strong></td>
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<tr>
<td>14:20-16:00</td>
<td>Panel and roundtable discussion</td>
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ABOUT IAS-ILF

The Industry Liaison Forum (ILF) is an initiative of the International AIDS Society (IAS) that brings together industry, independent investigators, non-governmental organizations, foundations and other stakeholders to enhance HIV prevention and treatment access and outcome in resource-limited settings. Founded in 2001, the IAS-ILF is part of the IAS’s Research Promotion Department, which includes the Journal of the International AIDS Society (JIAS), the Fellowships & Grants Programme, and Research Prizes & Awards. The IAS-ILF provides the platform for industry to engage, communicate and collaborate with other stakeholders to improve HIV research and health delivery for the benefit of populations that remain grossly underserved by the benefits of clinical progress.

The IAS-ILF has sought to fulfil its mission by: identifying research gaps; promoting targeted research; identifying challenges and best practices; disseminating information, conducting analyses; consulting and convening stakeholders; providing industry expertise; and supporting capacity building for research and health delivery. The IAS-ILF is exemplary of a unique collaboration between stakeholders in the global response to HIV/AIDS and serves as a platform for creative thinking and constructive dialogue around HIV research. The IAS-ILF Advisory Group consists of senior clinicians and public health experts from pharmaceutical and diagnostic industry, academia, non-governmental organizations, international organizations and UN agencies.

As part of its new Strategic Plan 2012-2014, the IAS-ILF will continue to prioritize prevention and treatment for women and children in resource-limited settings, with an emphasis on prevention and treatment outcomes, as well as access. The IAS-ILF will support research and other strategies to: enhance treatment management; scale up prevention of mother to child transmission programmes; improve prevention and treatment access and outcomes for these vulnerable populations; optimize the potential of pre-exposure prophylaxis and other chemoprevention interventions; and support best practices in public health policy and delivery.

For more information regarding IAS-ILF activities and its relevant publications, please visit our website at: http://www.iasociety.org/ilf.aspx.

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REFERENCES