



International AIDS Society – Industry Liaison Forum

DEFINING A RESEARCH AGENDA FOR WOMEN
IN RESOURCE-POOR COUNTRIES

3 February 2008, Boston

SUMMARY MEETING REPORT

EXECUTIVE SUMMARY

Pedro Cahn welcomed participants and opened the meeting with a brief presentation that described the rationale for ILF's priority focus on women. Pedro informed the group that having addressed the issue of PrEP, ILF was now focusing on a new priority area. Following extensive consultations with the ILF Advisory Group and ILF members including industry, clinical research priorities as they apply to women had been the overwhelming consensus for the ILF to address over the next two years. The issue of pediatrics is also integrated but it was agreed that this meeting would focus on research and treatment priorities affecting women with HIV, particularly in resource-limited settings.

Why women?

Pedro Cahn, Argentina and ILF Co-Chair

Pedro began with a basic epidemiology update noting that over 50% of new infections last year occurred in women. Pedro also emphasized the trend among young people and the vulnerability of young women in particular. He shared UNAIDS data that reported a positive trend in prevalence among pregnant women in some countries including Botswana, Ivory Coast, Tanzania, Kenya and Zimbabwe. While there was an increasing coverage for PMTCT, the figure has nominally increased from 3% to 9% between 2003 and 2005. Pedro also noted a number of other issues, including the fact that in many countries, the age of sexual debut is decreasing and that in the Caribbean, less than 30% of the youth population (15-24 years) has ever had an HIV test. Reporting from US CDC figures on the domestic pandemic, Pedro confirmed the rates of infection continues to remain high among Black and Hispanic communities. The proportion of women in the US by transmission category in the same year also confirms that high-risk heterosexual contact accounts for 71% of new infections. Pedro then outlined the treatment experience of women globally, noting their special vulnerability, including increased social, access and biological risks. **(full list of risks outlined in appendix 1)**

He further added that while the percentage of women actually receiving antiretroviral therapy was increasing and reached on average about 60% of women who needed treatment, it fell short of the expected target for coverage. He pointed out notable poor examples such as Ethiopia and Ghana where the coverage for treating women is 30% and 40% respectively. Referencing a presentation from last year's CROI, Pedro confirmed that even those women who can access therapy, due to late initiation or premature discontinuation of HAART, many women failed to benefit, losing significantly more years of life. Finally, Pedro closed his presentation commenting on the fragmentation of families and communities as a result of the HIV epidemic, observing that 9% of children in Sub-Saharan Africa have lost at least one of their parents; by 2020 the number of orphans in the region is estimated to be 20 million.

Epidemiological update on HIV and women

Quarraisha Abdool Karim, South Africa

Quarraisha Abdool Karim from University of KwaZulu-Natal and Columbia University in New York, followed Pedro in setting the context for the scientific presentations by describing the HIV prevalence and AIDS-related mortality in women. Quarraisha noted both the African and in particular, the South African demography. She emphasized the age and sex distribution of HIV prevalence and the classic distribution of HIV by gender and age seen throughout Africa. Quarraisha added that young women are increasingly infected at much greater rates than young men. Quarraisha explained that this is best explained by an age differential between young women and their male partners. Quarraisha elaborated that there are many reasons why young women engage in sex with older men, including economic necessity, family and social pressures, coercion and the desire for material goods. **(age, gender distribution and incidence outlined in appendix 2)**

Tuberculosis as a one of the leading causes of death globally was highlighted by Quarraisha with rates of coinfection with HIV proving to be a significant co-morbidity and concern for Africa. She concluded by stressing that we have yet to see the same benefits of HIV treatment in Africa at a

population level that we have clearly observed in the resource-rich world. She attributed this to the slow scaling up efforts of HIV therapy in the region noting the unmet need in many countries.

Research and treatment priorities for women in developing countries Purnima Madhivanan, India

Purnima Madhivanan from the Public Health Research Institute of India and University of California Berkley outlined priorities for research and treatment as observed 'through the gender lens'. Purnima highlighted the moving case of a patient from her clinic in Chennai. Kavita's case helped to illustrate the typical profile of a patient who presents with multiple symptoms and co-morbidities as well as the pressures of her gender from a society that severely disadvantages women. Kavita first presented with severe thrush, HIV wasting, fever, diarrhea, anaemia, reduced levels of haemoglobin and hematocrit. Her weight had fallen to less than 60 pounds. Laboratory testing showed CD4 count of 130 and her Total Lymphocyte Count <1000. Given the limited choice of treatments available and her ill-health, it was a challenge to find an easy, tolerable and potent regimen. Kavita complained that her home-life made it difficult to find the privacy to take her medication, and her heavy workload made it difficult remember to take all the different tablets. She was depressed and during each visit would complain of chronic nausea, vomiting, and fatigue. She died four months after her first visit. She was survived by her three children, one of which was HIV positive.

When it comes to health risks, Purnima suggested, sex does matter. Women are twice as likely as men to be affected by multiple sclerosis, rheumatoid arthritis and migraines. They are also more likely to have cataracts, thyroid disease and be infected with hepatitis. Women experience depression at double the rate compared to men. Women are also more biologically and socially susceptible to HIV infection. They have a more rapid progression of illness than men and present with a different constellation of opportunistic conditions. While much of the difference can be attributed to tendency of women to receive less care and to present with more advanced disease, researchers have found sex-based differences in women that affect the progression of their disease. (Bush, 1996; Evans, 1997; Farzadegan, 1998) Purnima noted that men and women are also different in ways that go beyond their reproductive systems including hormones and bone structure. They acquire many of the same diseases, but they may have different symptoms and their diseases may progress differently. They may for a number of reasons, also respond differently to treatment. Researchers from the US FDA examined 300 drug applications submitted to the agency between 1994 and 2000. More than half of these applications contained information on the effect of gender on pharmacokinetics and in more than 20% of drugs submitted in applications, the pharmacokinetics were different depending on gender.

Purnima then outlined some of the challenges:

- ◇ regimens poorly suited to the lifestyles and needs of women in developing countries
- ◇ lack of therapies geared to the unique treatment challenges posed by women
- ◇ human rights climate that devalues women

Purnima described a number of reasons why women such as Kavita may not have the same opportunities to life that many men suffering from HIV disease in India may have. She was a woman living in a system that devalued her worth as a person. She not only suffered from chronic nutritional deficiencies that made her vulnerable to disease but she had also simply not been given the care she needed at a time when it might have made a difference. More importantly, she faced additional challenges when she did eventually access care:

- ◇ available therapies and appropriate regimens not been developed with women like Kavita in mind
- ◇ adherence complicated by lifestyle and the heavy stigma associated with HIV disease in India
- ◇ low hematocrit levels assured a poor prognosis on drugs like AZT, the only affordable choices
- ◇ low weight and poor health made correct dosing difficult; a common challenge for HIV physicians

Purnima stressed that Kavita's case was not unique. Recent UNAIDS/WHO estimates place the number of people living with HIV in India at 2.5 million of whom 40% are women. 36% of Indian

women have a BMI below 18.5 indicating a high prevalence of nutritional deficiency. Anaemia is endemic among Indian women; 56% of all women suffer some form.

Why do we know so little about women and their experience of HIV, asked Purnima. She noted that we may essentially need to question what we understand about HIV given the profound under-representation of women in clinical trials. "The evidence basis of medicine may be fundamentally flawed because there is an ongoing failure of research tools to include sex differences in study design and analysis. The reporting bias which this methodology maintains creates a situation where guidelines based on the study of one sex may be generalized and applied to both." (Journal of the Royal Society of Medicine, January 2007) Almost 14 years after the US NIH issued guidelines for the study and evaluation of gender differences in clinical trials, we are still struggling to enrol adequate numbers of women in research studies. A systematic review was conducted of clinical trials published in the New England Journal of Medicine for the years 1994 to 1999. It found that in 120 randomized control trials, on average, only 24.6% women were enrolled. Gender specific data analysis was performed in only 14% of the trials. (K. Ramasubbu, H. Gurm, D. Litaker. Journal of Women's Health & Gender-Based Medicine, 2001). This could be one reason why in the last decade 8 out of the 10 prescription drugs were withdrawn from the US market because they caused statistically greater health risks for women than men. (Science, June 10, 2005)

The reasons given for this apparent disinterest are surmountable with the right commitment.

- ◇ ethical issues; but is it not unethical to subject women to drugs for which there are unknown risks, for example hormonal variations that may confound response and therapeutic outcomes.
- ◇ risk of pregnancy; investigators perceive that it will not be possible to enrol women of reproductive age in countries like India. They will be harder to access and study retention would be low for cultural reasons. The truth Purnima added, was simply that adequate numbers of women have not been enrolled because there has not been the will. She described her own experience of a study in which almost 1,000 women were recruited and followed for a year with 90% retention rates. It can and must be done, she concluded.

Purnima suggested a number of issues and questions for research that would promote a better understanding of how HIV affects women:

- ◇ feasibility of ARV treatment to prevent postnatal HIV transmission by studying PK of breast milk
- ◇ still not clear whether exposing infant to ARVs through breast milk causes developmental delays or severe side effects. Most information on safety of ARVs for pregnant women and infants comes from research in resource-rich settings where most HIV-infected women do not breastfeed.
- ◇ only a quarter of studies have human data to support findings in spite of the fact that in India alone, 100,000 HIV infected women will deliver children each year and most will breastfeed.

We need to understand better:

- ◇ understanding barriers to treatment-seeking for HIV among women in developing countries
- ◇ unique adherence challenges for women in resource-poor countries
- ◇ differences in sex and race and implications for pharmacokinetics and drug absorption
- ◇ impact of hormones on treatment and prognosis for women with HIV
- ◇ genital tract immunology in relation to HIV disease
- ◇ increased risk of lactic acidosis and hepatic steatosis in women
- ◇ clinical relevance of lower triglycerides and higher intracellular triphosphate levels on prognosis

Purnima concluded by noting some positive examples of clinical trials where a concerted effort is made to enrol and follow-up women, including HERS which has contributed epidemiological information on HIV in women and the Tibotec GRACE study testing darunavir in women. She noted the shallowness of our understanding regarding ARVs and women. What little we know comes from developed countries and may not always be applicable to poorer settings. She stressed that HIV has become an increasingly feminised disease and as such there were clinical, political and moral imperatives to making research more relevant. Risks should be managed, challenges faced and the same diligence and political will applied to understanding the implications of HIV in women. **(slides of studies that confirm or lack human data and paucity of trials in women attached as appendix 3)**

Clinical pharmacology of antiretroviral therapy in women Angela Kashuba, USA

Angela Kashuba from North Carolina, Chapel Hill presented a detailed overview of the pharmacologic complications that impact on HIV therapy, particularly in women. She noted given Purnima's presentation that most of the data that she would be presenting comes from research largely conducted in Caucasian women, and less in African-American. She confirmed that very little is understood of variability as a result of ethnic and racial phenotype. Angela described the constellation of factors that affect drug response, inter and intra-patient variability, including covariables such as gender, age, diet, smoking, pollution, and disease pathology (full list attached as appendix 4). Angela noted that potential sex differences in pharmacokinetics including the impact of menstrual cycle and menopausal changes in PK, interactions with contraceptive drugs, pregnancy-associated changes in PK and penetration of drugs into breast-milk as a factor for transmission. She described the differences in PK activity between men and women, noting the differences in absorption, distribution, metabolism and excretion of drugs.

Angela reported that there were no consistent differences in absorption, although women have lower gut alcohol dehydrogenase activity. Additionally, there has been some suggestion of higher CYP3A activity and lower P-glycoprotein activity in the female gut, although since many compounds are substrates for both sets of proteins, these activity differences may negate each other. Some small sex differences in protein binding may occur, but are not considered to be enough to significantly change the volume of distribution or affect free drug exposure. As for elimination, or drug clearance, any significant differences between men and women are generally negated once adjusting for body weight ($CL = mL/min/kg$). This suggests that for most women, increased exposure (and perhaps increased toxicity) is due to a similar dose being used in an individual of smaller body weight. This is particularly important for drugs that have narrow therapeutic indices.

Angela provided an overview of drug concentrations in women in the different classes of antiretrovirals. She noted that the literature was relatively confusing with studies based on small numbers and demonstrating conflicting results. She showed fold-increase in intracellular concentrations of phosphorylated N(t)RTIs perhaps explaining the increased toxicities experienced by women with some NRTIs. Significant differences have not been seen in the extracellular plasma concentrations zidovudine (AZT), lamivudine (3TC), tenofovir (TDF) and stavudine (d4T). Abacavir (ABC) and didanosine (ddI) are not well characterized.

However, there were significant differences in NNRTI pharmacokinetics in women compared to men. A number of studies have shown that nevirapine (NVP) exposure was greater in women; two studies showing 22- 50% higher concentrations, one study showing 25% lower exposure and two studies demonstrating no difference. For efavirenz (EFV), one study showed 30% higher concentration, one resulted in 25% lower levels and two other studies showed no impact of sex.

Sex differences in PIs have been reported to lead to higher concentrations in women with four studies noting a 2-fold difference and one trial confirming a 25% increase in exposure. No significant differences were found for lopinavir (LPV), indinavir (IDV), ritonavir (RTV), amprenavir (APV) and nelfinavir (NFV), but slightly elevated exposures were observed with tipranavir (TPV) and darunavir (DRV). Lopinavir has demonstrated a sex difference, but Courtney Fletcher reported at CROI 2007 that disposition was similar when adjusted for body weight. However, in examining lopinavir trough concentrations, more diurnal variability may be seen in women than in men. Angela then described the impact of gendered differences such as menstruation, menopause, pregnancy and interactions with oral contraceptives on the pharmacokinetic profiles of antiretrovirals (tables outlining drug disposition across the menstrual cycle and effect of pregnancy on pharmacokinetics attached in appendix 4). She concluded that while menstrual cycle does affect drug disposition, it was not significant to warrant dosing adjustment. AAG is estrogen sensitive but no significant changes in protein binding has been observed during menstruation. Similarly, absorption, distribution,

metabolism and excretion mechanisms fluctuate during pregnancy, given the changes that occur in the concentrations of binding proteins and CYP activity.

Finally, from a drug compartmentalization perspective, antiretrovirals penetrate the genital tract of men and women in a similar hierarchy (eg NRTIs achieve the highest concentrations, relative to blood plasma, in both semen and cervicovaginal secretions), although the absolute amount of penetration may differ. (tables describing genital tract exposure attached in appendix 4).

Sex-specific drug interactions focused on ARVs and contraceptives. Angela pointed out that while we see some varied interactions, we still do not understand at what level of exposure contraception might fail. Without this knowledge, certain potentially useful combinations are avoided. Finally, regarding the pharmacology of ARVs in breast-milk and in breast feeding infants, Angela noted that most information is obtained in lactating rats, and that this information is not always able to be directly extrapolated to women. Additionally, we have little information on drug exposure and potential toxicity in breast fed infants.

Industry roundtable

Elly introduced Karen Manson from Tibotec, Vice President, Communications and Public Affairs, at Tibotec. Karen introduced and facilitated the industry roundtable session. She made some general observations from an industry perspective, commenting that HIV was first encountered as a white, male disease. This is no longer the case. Many of the studies have historically focused on treatment experienced patients and research needs to progress to reflect the changing profile of the epidemic. Industry recognizes this as an issue and this forum as one useful way to address these challenges.

On behalf of Tibotec, Karen presented an outline of the GRACE (Gender, Race and Clinical Experience) study established in 2006. The key criterion was that 70% of the trial participants had to be women with a recruitment period of 12 months. This was considered impossible at the time. The key learning for Tibotec from this study has been the need to move beyond large, established academic centres and explore new sites where working-class women and those from minority communities access care, and to collaborate with local AIDS service organizations as part of the pre-trial commitment. To recruit women into clinical trials requires a huge commitment and innovative approaches from industry.

Sibtain Rahim outlined Abbott's focus on research in developing world as largely investigator-initiated particularly related to PMTCT. These include a number of different strategies including short-course NVP, initiating therapy earlier in pregnancy, extending therapy to start at the second-semester and end after cessation of breast-feeding. Studies of breast-milk pharmacokinetic and resistance to NVP and to other components of triple drug regimens are also ongoing. Finally, Abbott is examining treatment options for women following PMTCT prophylaxis.

Thomas Fischer from Boehringer Ingelheim confirmed that NVP is one of the most studied drugs for PMTCT. Many of the studies are investigator-initiated with BI support. BI is currently supporting a study similar to GRACE investigating efficacy and safety of TPV in women from different racial communities.

Ann Kolokathis and Patricia Doykos from Bristol Myers Squibb noted the importance of recognizing that challenges are matched by opportunities for learning. BMS is involved with a number of studies with research agencies, government bodies and industry collaborators. BMS studies have consistently recruited and retained on average 25-30% of women and this has been the case since the 1990s. These numbers are expected to increase as scale up increases in the developing world. BMS is involved with paediatric studies of atazanvir; efforts not only focus on treatment but broader approaches that involves supporting women and families. Strategies under investigation include different models of family care, technical response, capacity-building, nutrition and transport.

Jim Rooney from Gilead noted that the good news is that increasing data will be forthcoming from a number of studies currently underway and these will have recruited greater numbers of women. ANRS and MRC have studies in Africa that involve recruiting large numbers of women, including studies that target only women such as those exploring treatment strategies for mothers exposed to PMTCT. Gilead has conducted studies such as the 903 trial that recruited 25% women, mostly from Latin America. A paediatric programme is also ongoing in Latin America. The majority of efforts however, are in collaboration with other groups including the MRC, ANRS, DAIDS, CDC and HIV-NAT in Thailand. Other studies involving 3-4,000 women on treatment containing TDF or Truvada will also deliver results soon. Gilead's commitment includes prevention studies such as PrEP, maternal-fetal transmission studies and paediatric trials. ACTG and HPTN 057 are planning dosing strategies for mothers and the ANRS are undertaking a study with Truvada in conjunction with NVP.

Discussion summary

Terry Blaschke from Stanford University asked if a great deal of sex-based variance be reduced if dosing were adjusted for body weight or body surface area. Angela Kashuba agreed that this appears to be the case. Correcting for body weight, the AUC per kilogram of clearance tends to normalize. Issues associated with intracellular concentrations however, might not be so readily explained, she added. Jean Anderson from Johns Hopkins University asked whether given the concerns about PK and ethnic differences was research is underway to address this. Angela confirmed that studies (such as 5202) will evaluate drug exposure over time and is powered to evaluate not only differences between men and women but across racial groups. The results from the study are not yet available. Myron Cohen from the University of North Carolina asked in relation to breast-feeding and toxicology, what signals could be observed from mouse toxicology models. Lynne Mofenson from the US National Institutes of Health responded that many studies do not focus on the infant but on breast-milk. Jim Rooney added that reproductive toxicology studies are undertaken by industry but these generally dose both mothers and infant, and do not necessarily involve studies of breast-milk concentrations.

Cate Hankins from UNAIDS informed the group that UNAIDS had held a meeting in December supported by industry called Making HIV Trials Work for Women and Adolescent Girls. She noted that industry had appeared somewhat surprised that NIH and FDA were developing guidelines for increasing enrolment of women into trials. Cate questioned industry as to the specific challenges to enrolling women into clinical trials. Again Jim noted the significant challenges to recruiting women including sensitivities of safety in pregnancy. Safety has to be established before trials up more broadly. This is not a challenge specific to industry. ACTG and other research agencies report the same obstacles. Beyond safety, there are practical challenges such as providing child-care and improving access. In the developing world, the situation may be more promising with some studies enrolling equal or greater numbers of women. For example the two-thirds of participants in the DART study are women.

Quarraisha Abdool Karim from University of KwaZulu Natal emphasized that we are dealing with a public health crisis and do not have the luxury of waiting for sequential drug development through the traditional pathway. Some populations are at greater risk than others; what is needed is to address the issue of different populations and impact of HIV and treatment on women. Lynne Mofenson noted a distinct gap in research on heterosexual acquisition in young women that is not being adequately addressed. Studies of microbicides and vaccines during pregnancy are needed, otherwise we will fail to learn about pregnancy and safety and lose women who are enrolled in prevention studies and become pregnant. The impact of drugs on breast-feeding, and the increasing need to continue treatment for 12-15 months during breast-feeding are critically important. What happens to the mother when drugs are stopped? What is the impact on HBV, and drug resistance? Finally, what is the impact of stopping drugs for PMTCT? NIH is planning a large study called PROMISE (Promoting Maternal and Infant Survival Everywhere) that incorporate many of the questions discussed here into one study.

Myron Cohen asked Elly and other Ugandan investigators who have demonstrated that HIV affects couples, many of whom are sero-discordant. This has huge public health implications. In discordant couples, as with any other, women may wish to become pregnant. In-vitro fertilization programmes developed in the US may be redundant given that the HIV pandemic in countries where this technology is not relevant. Rodney Kort from IAS reported on findings from another study presented at the IAS Pathogenesis conference last year enrolling a sero-discordant cohort of 50-60 couples who wanted to have children and were using TDF as prophylaxis. After one year, 33 couples were able to conceive and no transmission of HIV was reported.

David Haerry from the European Community Advisory Board noted that as activists, we continue to lobby industry to recruit more women. He suggested the development of computer-models to overcome the current bottleneck of safety, particularly in pregnancy. Lynn Paxton, US Centers for Disease Control and Prevention raised the role of Institutional Review Boards (IRBs) and their intrinsic reluctance to enroll women given pregnancy concerns. In CDC studies, she noted, they faced obstacles in enrolling adolescent girls. It is not only industry's problem. We have to resolve this issue with the IRB and establish a better system that enables us to study pregnant women. This needs to be set up and cleared through IRB before a trial starts, so that studies are not interrupted for 6 months if women become pregnant during the trial. Karen Manson from Tibotec confirmed that objections raised by ethics committees have been a significant obstacle to what we have been able to do in promoting recruitment of women. High number of women in studies who become pregnant in African countries remains a continuing challenge. While accepting that IRBs do provide a challenge, Bob Grant from the University of California San Francisco noted that these obstacles are surmountable. IRBs are evolving and amenable to discussion and change. Cate Hankins added that we already have experience from the vaccine field of studies in adolescents for example where, trials of safety and tolerability start while Phase I and Phase II are underway. Zeda Rosenberg from the International Partnership for Microbicides noted that the issue of pregnancy in microbicides trials has been a significant challenge, where women are on-study but off-drug, this could represent 10-20% of women not in the study at any given time. Providing contraception on site remains important and Zeda concluded that while this is an issue that needs to be resolved, it is certainly not a reason for not doing studies with women.

Bob Grant confirmed that expanding study sites promotes a greater engagement with a different range of populations. It is therefore time to consider conducting more pivotal studies, Phase II and Phase III at African sites. High-quality data can be collected given that we now have greater infrastructure in places such as Latin America and Africa. It may be that in future, FDA will not approve antiretrovirals that have not been studied in women. Rob Camp from the AIDS Treatment Activist Coalition reinforced the comment on identifying new sites for research. This will help bring an understanding of patients from a broader range of communities. It is unacceptable that historically we have not gathered information on women. An ACTG study of barriers to women recently showed that one of the significant barriers to recruitment was access to trial sites; having sites open after 5pm or on Saturday morning would help enormously.

In closing, Quarraisha Abdool Karim stressed that in her two decades of research experience, she had problems in recruiting women and this involved working with different communities and demanding research sponsoring bodies. Not all women fall pregnant, but many do and this should be understood within a cultural context. We certainly need to provide contraceptive services on-site. Quarraisha suggested that the challenge was not so much practical as one of political will.

SUMMARY CONCLUSIONS

- ◇ Women are more biologically and socially susceptible to HIV infection with a more rapid progression of illness and presenting with a different constellation of opportunistic infections.
- ◇ Women receiving antiretroviral therapy is around 60%, but falls short of expected targets. Notable examples of poor coverage are Ethiopia and Ghana with 30% and 40% respectively.

- ◇ Treatment regimens are often poorly suited to the lifestyles and needs of women in developing countries exacerbated by human rights conditions that devalue women.
- ◇ Reporting bias compromise women; guidelines based on study of one sex are generalized. A review of clinical trials found that of 120 randomized control trials, on average, only 24.6% women were enrolled and gender specific analysis performed in only 14% of trials.
- ◇ Factors that affect drug response and inter, intra-patient variability include gender, age, diet, smoking, pollution, and disease pathology.
- ◇ Theoretical mechanisms exist for sex-differences in PK, however, no compelling data to suggest altered ARV PK/exposure between men and women once corrected for body weight.
- ◇ Potential sex differences in pharmacokinetics include effect of menstrual cycle and menopausal changes, interactions with contraception, pregnancy and penetration of drugs into breast-milk.
- ◇ Intracellular concentrations of some N(t)RTIs are found to be higher in women and might explain increased toxicities with some NRTIs.
- ◇ There are some significant differences in NNRTI pharmacokinetics observed in women compared to men.
- ◇ Sex differences are also reported for some PIs accumulating in higher concentrations in women.
- ◇ Menstrual cycle affects the disposition of some drugs, but not enough to warrant dosing adjustment.
- ◇ Genital tract concentrations between men and women confirm that drugs that concentrate in men also penetrate female genital tract.
- ◇ Relevance of altered ARV PK in pregnancy is unknown but currently under investigation
- ◇ Pharmacology of breast-milk and infants suggests differences in exposure as observed from lactating rats; 3TC, NVP and NFV concentrate differently in plasma, breast-milk and infants.
- ◇ Tibotec GRACE trial testing darunavir set a target of 70% women; key learning from study was the need to move beyond large academic centres to explore new sites accessible to women.
- ◇ Abbott is focused on PMTCT studies including strategies for short-course NVP, early initiation of therapy, breast-milk PK and resistance and treatment for women following PMTCT prophylaxis.
- ◇ Boehringer Ingelheim continues to support PMTCT studies with NVP. BI is currently supporting a study similar to GRACE investigating TPV in women from different racial communities.
- ◇ Bristol Myers Squibb are supporting studies that address different models of family care, technical response, capacity-building, nutrition and transport as a way of promoting engagement of women in research and treatment.
- ◇ Gilead 903 trial recruited 25% women. Gilead commitments include PrEP, PMTCT and pediatrics; majority of efforts are in collaboration with others such as MRC, ANRS, DAIDS, CDC, HIV-NAT.
- ◇ Issue of pregnancy during trials is a major challenge for many investigators; studies of microbicides and vaccines during pregnancy are needed.
- ◇ Impact of drugs on breast-feeding and the increasing need to continue treatment for 12-15 months during breast-feeding is important and needs investigation.

- ◇ Studies in sero-discordant couples are critical for resource-poor settings.
- ◇ Evolving role of IRBs is critical in determining inclusion of women. Experience from vaccine studies suggests that trials of safety can be started while Phase I/II are underway.
- ◇ It may be that in future, FDA will not approve antiretrovirals not studied in women.
- ◇ Barriers to recruiting women include practical help such as late or weekend access and childcare.

Elly closed the meeting by thanking the speakers, industry representatives, organizers and delegates. The next meeting will take place in Mexico City during the International AIDS Conference and will be organised by Shirin Heidari at IAS.

Participants

Pedro Cahn, Fundación Huesped and IAS, Argentina (IAS-ILF Co-Chair)
 Elly Katabira, Makerere University, Uganda (IAS-ILF Co-Chair)
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 Adriana Andrade, Johns Hopkins University, USA
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 Terry Blaschke, Stanford University, USA
 Loida Bonney, Emory University, USA
 Rob Camp, AIDS Treatment Activist Coalition, USA
 Myron Cohen, University of North Carolina, USA
 Carl Dieffenbach, NIH, DAIDS, USA
 Rob Dintruff, Abbott, USA
 Patricia Doykos, BMS, USA
 Ernest Ekong, Military Reference Hospital, Nigeria
 Thomas Fischer, Boehringer-Ingelheim, Germany
 Mary Glenn Fowler, Johns Hopkins University, USA
 Bob Grant, University of California San Francisco, USA
 David Haerry, European AIDS Treatment Group, Switzerland
 Cate Hankins, UNAIDS, Switzerland
 Marjan Hezareh, AIDS Research Alliance, USA
 Angela Kashuba, University of North Carolina, Chapel Hill, USA
 Lynne Kenney, Merck, USA
 Ann Kolokathis, BM, USA
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 Ron MacInnis, IAS, Switzerland
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 Sibtain Rahim, Abbott, USA

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Jim Rooney, Gilead, USA
Zeda Rosenberg, International Partnership for Microbicides, USA
Paul Schaper, Abbott, USA
Virginie Supervie, University of California Los Angeles, USA
Linda Sussman, International Center for Research on Women, USA
Mark Wainberg, McGill University, Canada
Chris Woodward, Abbott, USA
Sheryl Zwierski, NIH, USA

Apologies: Joep Lange, ILF Co-Chair, Louise Martin-Carpenter, GSK, Malte Schutz, Roche.



Appendix 1

Why women? Pedro Cahn, Argentina and ILF Co-Chair

Factors describing women's vulnerability to HIV infection.

Biological risk

- ◇ Unprotected sex
- ◇ Anal sex as contraceptive
- ◇ STD
- ◇ IUD
- ◇ Cervical ectopy in adolescents
- ◇ Uncircumcised partner
- ◇ HPV/Cervical cancer
- ◇ Overall higher risk per unprotected contact

Social risk

- ◇ Limited room for negotiation
- ◇ Economic dependence
- ◇ Education
- ◇ Violence
- ◇ Sex work
- ◇ Drug and alcohol abuse
- ◇ Cultural barriers
- ◇ Caregiver role
- ◇ Attention limited to pregnancy and commercial sex work
- ◇ Neglect of human rights issues

Access

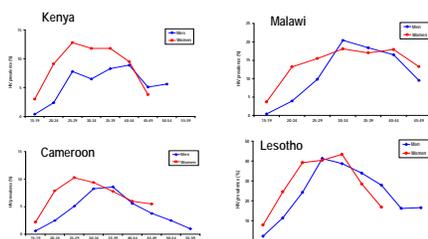
- ◇ Underserved in prevention and treatment programs
- ◇ Situation exacerbated in ethnic minorities and rural communities
- ◇ Under represented in clinical trials
- ◇ Pharmacology issues including PK in pregnant women

Appendix 2

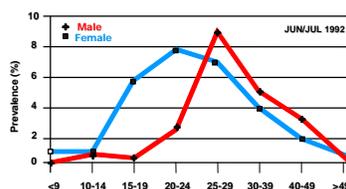
Epidemiological update on HIV and women: Quarraisha Abdool Karim, South Africa

HIV in South Africa.

HIV prevalence by age and sex

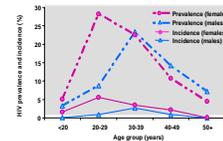


Age and gender distribution of HIV infection in South Africa



Source: Abdool Karim Q, Abdool Karim SS, Singh B, Short R, Ngongno S. AIDS 1992; 6: 1535-9

HIV incidence and HIV prevalence by age and sex, South Africa 2005



Source: Rakiti T, Shisana O, Pillay V, Zuma K, Puren A, Parker W. National HIV incidence measures: new insights into the South African epidemic. South African Medical Journal 2007 (in press)

Slow scaling up of ART in sub-Saharan Africa

Country	Upper estimate of number on ART	Coverage (%)	Unmet need*
South Africa	138,000	14	866,000
Nigeria	48,000	8	598,000
Zimbabwe	16,000	5	308,000
Tanzania	9,500	3	307,000
Ethiopia	19,000	7	261,000
Kenya	46,000	17	233,000
Mozambique	13,000	6	204,000
DRC	6,000	3	203,000
Zambia	33,000	18	153,000
Malawi	23,000	14	150,000
Total	351,500	±10%	3,283,000

*number of people aged 0-49 in need of ART in 2005 less the estimated number treatment by June 2005
Source: The WHO reproductive health library. Reproductive Health Library informing best practice in reproductive health. 2005

What do we need to understand better?

Drug	Animal Studies	Human Studies	Comments
Abacavir (ABC)	Yes (rats)	Unknown	
Zidovudine (ZDV)		Yes	BM 2-3 times higher than serum
Didanosine (ddI)	Yes (rats)	Unknown	
Emtricitabine (FTC)	Unknown	Unknown	
Lamivudine (3TC)		Yes	BM 2-3 times higher than serum
Stavudine (d4T)	Yes (rats)	Unknown	
Tenofovir (TDF)	Yes (primates)	Unknown	Peak 3%, AUC 20% of serum
Efavirenz (EFV)	Yes	Unknown	
Nevirapine (NVP)	Yes	Yes	BM/plasma ratio 61-71%
Amprenavir (APV)	Yes (rats)	Unknown	
Atazanavir (ATV)	Yes (rats)	Unknown	
Indinavir (IDV)	Yes (rats)	Unknown	BM/plasma ratio: 90-540%
Lopinavir (LPV)	Yes (rats)	Unknown	
Nelfinavir (NFV)	Yes (rats)	Yes	BM/plasma ratio: 6-24%
Saquinavir (SQV)	Yes (rats)	Unknown	

Source: Mofenson LM. HIV Transmission through Breast-Feeding. March 2006 [In press].

Are we making progress?

- GRACE, SIMBA study
- Total number of trials registered with clinicaltrials.gov: 3,335

	# of trials	Trials with women
Africa	329	76 (23%)
Central America	357	84 (23.5%)
East Asia	72	4 (5%)
Middle East	42	4 (9%)
North Asia	21	4 (19%)
South America	178	25 (14%)
South Asia	40	9 (22.5%)
South East Asia	122	17 (14%)

Appendix 4

Clinical pharmacology of antiretroviral therapy in women: Angela Kashuba, USA

Factors that affect drug response:

Individual	gender, age, diet, liver/renal functions, albumin, smoking, alcohol
Environmental	smoking, pollution, occupational exposure
Population	infection rates, immunization, circadian and seasonal variations
Disease	infectiousness, disease pathology and progression, treatments

Impact of menstruation, menopause, pregnancy on the pharmacokinetic profiles of antiretrovirals.

ADM Kashuba ILF 2008

Drug Disposition Across the Menstrual Cycle

- **Absorption**
 - overall, lack of clinically significant changes (EtOH)
- **Distribution**
 - AAG is estrogen sensitive, but no sig protein binding changes for: nitrazepam, phenytoin, phenobarbital, carbamazepine, Na salicylate
- **Metabolism**
 - varying data on P450 enzyme activity
 - nonspecific substrates have ↑ clearance at ovulation with ↓ clearance in luteal phase, but most data show variations insignificantly 3-15%
 - little data on Phase II
 - AZT clearance increased 14-16% at, and post, ovulation
- **Excretion**
 - ↑ vasopressin, renin and aldosterone in luteal phase, but no significant changes in GFR

Menopause and ARV

Distinct implications for older women becoming HIV-infected and infected women becoming older.

No reports assessing PK in peri and post-menopausal women.

Enzymes and proteins under hormonal control.

Increased fluctuations may increase drug exposure variability and alter toxicity and efficacy profiles.

Lack data on genital tract penetration during menopause.

Effect of Pregnancy on Pharmacokinetics

Absorption	↓ Cmax and ↑ Tmax 30-50% ↓ intestinal motility (↑ progesterone) 40% ↓ gastric acid secretion (↑ pH) alters ionization/absorption of weak acids and bases
Distribution	↑ Vd and ↓ drug concentrations 8L ↑ in total body water, 50% ↑ plasma volume ↓ albumin binding (dilutional &/or competitive inhibtn with corticosteroids) ↑ free fraction seen with theophylline, salicylates, equivocal effects on AAG
Metabolism	↑ or ↓ drug exposure ↑ activity (d/t ↑ progesterone) ~ 50% ↑ in CYP2C9, CYP3A, UGT; ~100% ↑ in 2D6 ↓ activity (competitive inhibtn with estrogen and progesterone) ~ 50% ↓ in CYP2C19, CYP1A2 cholestasis with drugs eliminated through bile (d/t estrogen)

Excretion 1st trimester ↑ cardiac output, with 50% ↑ GFR (up to 65%)

