



**Gender and science:
Shifting the paradigm in HIV research**

MEETING REPORT



Public Satellite Session at AIDS 2012
Washington, DC, USA
23 July 2012

“Back in the '80s when the epidemic violently exploded, the very first successful information, education and prevention campaigns in Africa were those led by brave women. Since then women have borne the burden disproportionately. Combating harmful social norms, promoting gender equality, empowering women is essential to boost HIV response for women and girls. We must also take more consideration of women in research to address specific questions related to HIV infection in women and increase their representation in clinical trials.”

Closing speech, AIDS 2012, 27 July 2012

Françoise Barré-Sinoussi

IAS President

INTRODUCTION

Historically, health research has not systematically accounted for sex and gender differences, starting from the infancy of study design all the way through to the publication of findings. In the field of HIV, a matrix of social, ethical, policy and regulatory factors have contributed to women's historical exclusion and underrepresentation in research, particularly in the area of clinical research. As health outcomes can differ between men and women, the importance of accounting for sex/gender differences is increasingly being appreciated as part of evidence-based prevention, treatment and care.

In 2010, the International AIDS Society-Industry Liaison Forum (IAS-ILF), with 15 other organizations (including WHO, UNAIDS, pharmaceutical companies, non-governmental organizations and community groups) jointly released the 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. Notably, one of the key recommendations emphasized that research data should be disaggregated by sex. Since the publication of the Consensus Statement, the *Journal of the International AIDS Society* (JIAS) introduced an [editorial gender policy](#), which encourages submitting authors to include data disaggregated by sex and to provide a gender analysis when appropriate. *The Lancet* introduced a similar policy at the end of 2011.

As part of a continuing effort to promote HIV clinical and operational research in women, the IAS-ILF and The Foundation for AIDS Research (amfAR) co-organized a public satellite session at the XIX International AIDS Conference (AIDS 2012) aimed at offering insight into how a gender-based approach to research can translate into better science, and how gender-sensitive HIV research itself can lead to enhanced clinical management of women and men living with HIV. The session included a series of presentations by experts, followed by a panel discussion, where the roles and responsibilities of researchers, as well as funding agencies, journal editors and advocates, were addressed. The end objective of this session was to ensure that participants departed with a better understanding and justification for a paradigm shift in the conduct of more gender-sensitive research.

The session was co-chaired by Shirin Heidari (Senior Manager, Research Promotion Department, IAS) and Rowena Johnston (Vice President and Director of Research, amfAR), who jointly provided opening remarks. Heidari presented a background of the IAS-ILF's mission and efforts to accelerate HIV clinical research in women, underscoring how women are both biologically and socially more susceptible to HIV infection. A growing body of evidence has been demonstrating how sex and gender affects HIV acquisition/transmission, disease progression, and treatment outcomes. In highlighting women's participation in clinical trial research, Johnston presented data (Figure 1) that illustrates how women are currently being underrepresented in HIV cure research trials.

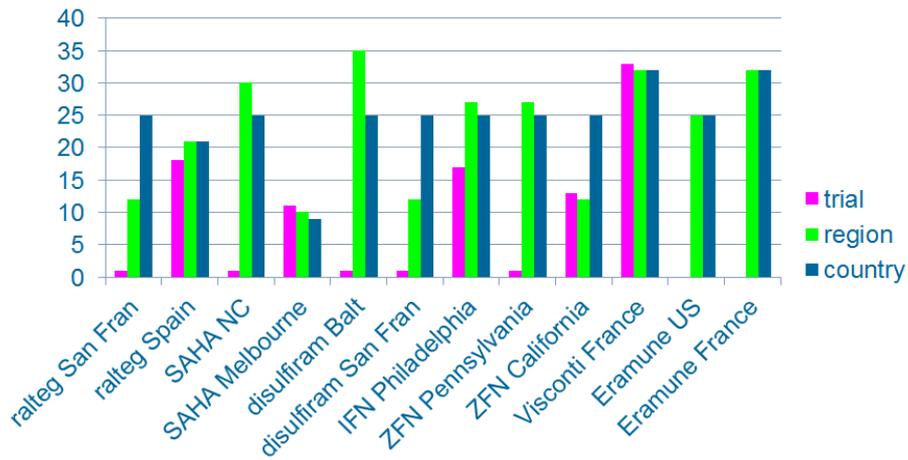


Figure 1. Percentage of women participating in Phase I HIV cure research trials

What are the differences between women and men in the context of HIV? From transmission to treatment

Linda-Gail Bekker, Desmond Tutu HIV Centre, University of Cape Town, South Africa

As the first invited speaker, Linda-Gail Bekker underscored the important complexities between sex and gender in HIV infection, echoing the UNAIDS approach to “knowing your epidemic” by highlighting country-to-country variation across key populations (Figure 2). Bekker called for the need to undertake in-depth studies in what she described as a “moving” epidemic, with HIV being dynamic from an epidemiological and social standpoint. In the context of HIV infection, she also highlighted that sex and gender matter across all areas of epidemiology, transmission, treatment responses, opportunistic infections and prevention efforts.

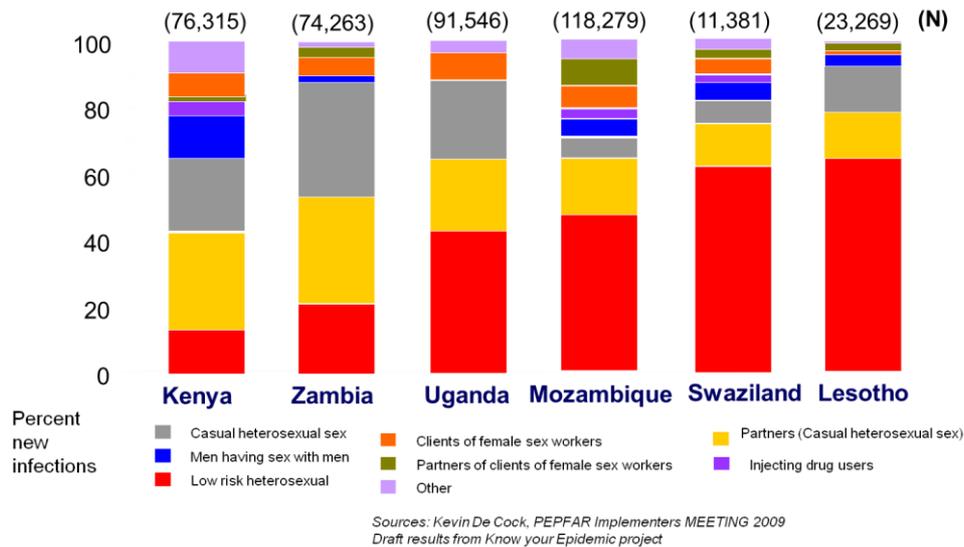


Figure 2. HIV incidence by modes of transmission across six sub-Saharan African countries

Globally, more women are infected/living with HIV than men (15.7 million women versus 15.3 million men). Married women are most at risk for HIV infection in some countries, such as Uganda, and young women of reproductive age are at particular risk in southern Africa countries. In some models, in particular one reported from South Africa, the proportion of women at risk for HIV acquisition by the age of 60 could be as high as a staggering 60%; this highlights that the needs of women in different age groups should be taken into consideration. A gender-based approach is “not just about women”, Bekker noted, and provided data from a Cape Town township, where men who have sex with men (MSM) are at extraordinary risk for HIV-I infection and where HIV-I prevalence was estimated at 40% for men who are 20-29 years of age.

Beyond Africa, Bekker touched upon the HIV epidemic in Asia, with provocative data showing condom usage being virtually non-existent among female Burmese migrants when compared with Thai nationals¹. She emphasized the need for constant surveillance of new HIV cases and for flexibility in responses, coupled with optimized design of prevention packages. In terms of transmission risk, Bekker outlined the biological factors associated with increased susceptibility to HIV infection in women, such as cervical ectopy and the peripartum period. She also pointed out that there are outstanding research questions about the impact of hormonal contraception regarding transmission and acquisition risk. Notably, the findings by Heffron and colleagues published on 4 October 2011 in *The Lancet Infectious Diseases* suggested that the use of hormonal contraception may increase the risk of acquiring HIV infection two-fold². Bekker underscored the need for more data on pregnant women living with HIV, and emphasized that their participation in clinical trials remains critical.

The factors resulting in sex or gender differences in health outcomes between men and women are complex. For example, in a study conducted in South Africa, men living with HIV have a higher risk of mortality, while women appeared to have comparatively higher CD4+ counts. Bekker addressed gender differences in adverse events profiles, with women on ART suffering more from rash and lipid abnormalities. In addition to physiological/biological differences, there is an ever-growing sense of the social and structural factors (e.g., access, screening) that contribute to differences in risk and health outcomes between men and women. Bekker concluded with a call for constant vigilance in understanding sex differences, also in the areas of prevention, such as PrEP research, and in vaccine efficacy studies.

¹ Mullany et al, *AIDS Care*, 2003; Lertpiriyasuwat et al, *AIDS*, 2003; Leiter et al, *Health & Human Rights*, 2006.

² Heffron R, Donnell D, Rees H, Celum C, Mugo N, Were E, de Bruyn G, Nakku-Joloba E, Ngunjiri J, Kiarie J, Coombs RW, Baeten JM; Partners in Prevention HSV/HIV Transmission Study Team. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis*. 2012 Jan;12(1):19-26. Epub 2011 Oct 3. Erratum in: *Lancet Infect Dis*. 2012 Feb;12(2):98.

Why gender analysis matters in science

Londa Schiebinger Director, EU/US Gendered Innovations in Science, Health & Medicine, and Engineering Project;
John L Hinds Professor of History of Science, Stanford University

Londa Schiebinger from Stanford University provided insight into why sex and gender analysis is critical in scientific research. Noting that there is a business case for a gender-sensitive approach, Schiebinger indicated that between 1997 and 2000, 10 drugs were withdrawn from the US market because of life-threatening health effects, with four of those drugs having greater adverse effects in women³. However, as most human clinical research for drugs is conducted primarily in males, sex differences in adverse events go unnoticed. Interestingly, this trend persists even in experiments involving tissues, cells and animal models. Beery and Zucker spoke about the proportion of articles reporting the sex of animal used in experiments in biomedical journals: the majority were male (Figure 3)⁴. Schiebinger also presented data from Taylor and colleagues, who surveyed the top 10 cardiovascular journals and reported on the proportion of articles indicating the sex of cells used in experiments (with the majority not specifying sex, or indicating use of male cells)⁵.

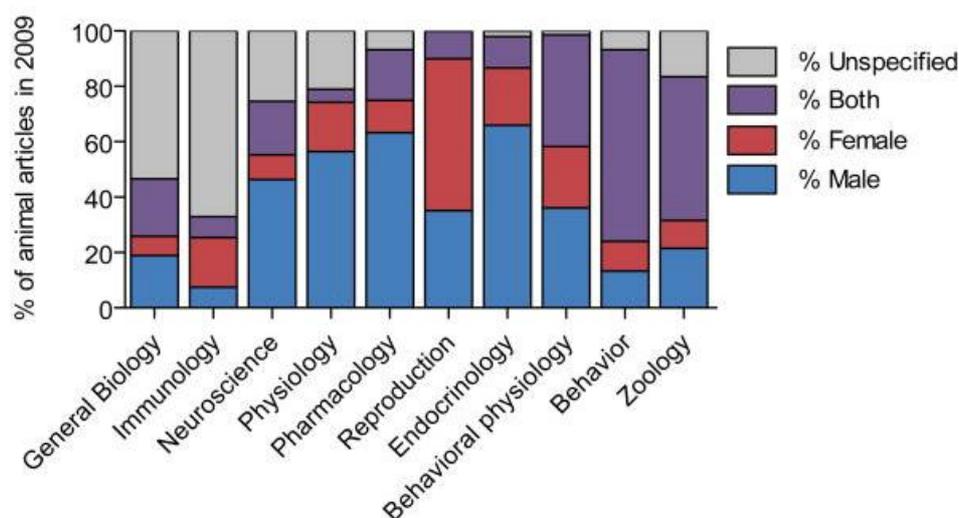


Figure 3. Proportion of 2009 journals reporting sex of animals used (Beery and Zucker, 2011)

Schiebinger advocated for the need to identify gender bias and understand how it operates in science and technology, and commented on how analysis by sex/gender should be conducted prospectively (in other words, designing it into the study from the beginning) (Figure 4). The rationale underlying this approach is linked to the notion that new knowledge and technologies can be stimulated. Schiebinger described sex and

³ United States General Accounting Office (GAO) (2001). Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women. Washington, D.C.: Government Publishing Office (GPO).

⁴ Beery A, Zucker I (2011). Sex Bias in Neuroscience and Biomedical Research. *Neuroscience and Biobehavioral Reviews*, 35 (3), 565-572.

⁵ Taylor K, Vallejo-Giraldo C, Schaible N, Zakeri R, Miller V (2011). Reporting of Sex as a Variable in Cardiovascular Studies using Cultured Cells. *Biology of Sex Differences*, 2 (11), 1-7.

gender analyses as additional “controls” (or filters for bias) in elevating the standard of excellence in sectors of medical research, policy and practice.

Schiebinger proceeded to offer an overview of the Gendered Innovations project, which started in 2009 as an initiative at Stanford University, and is currently funded by Stanford University, the European Commission for Research & Innovation, and the National Science Foundation. Gendered Innovations has an online platform, <http://genderedinnovations.stanford.edu/>, providing researchers with peer-reviewed tools that are needed when designing studies, along with case studies with concrete examples of how sex/gender analyses can enhance scientific outcomes. In one notable case study, those interested in HIV microbicide research are shown why it is important to investigate not only the fluid mechanics of the product being investigated, but also how sexual practices can differ between women and across populations (e.g., some cultures value dry sex, with implications for uptake of a microbicide).



Figure 4. Sex/gender analysis is relevant across the full spectrum of research

The Gendered Innovations website also addresses policy, as it is linked to funding and research priority setting. Interestingly, the website includes the policies of major granting agencies requiring applicants to include sex and gender consideration in their proposals, where appropriate, as a prerequisite to receive funding. Schiebinger commented on how the European Commission has been especially progressive in having such a policy in place (e.g., researchers applying for funding are asked to indicate “whether, and in what sense, sex and gender are relevant in the objectives and in the methodology of projects” [European Commission, 2003]. The Gendered Innovations website also maintains a running list of policies of peer-reviewed journals requiring authors to report the sex of organisms /subjects studied and/or gender analysis in submitted manuscripts.

In closing, Schiebinger made an emphatic point that the cost of accounting for sex/gender (and having adequate representation of females) in the experimental stage is minimal compared with the cost of drugs that fail when given to women.

Gender and science: shifting the paradigm of HIV research

Joy Johnson, Scientific Director, Canadian Institutes of Health Research, Institute of Gender and Health

As the architect of a practical guide to design and conduct sex/gender sensitive research, Joy Johnson from the Canadian Institutes of Health Research (CIHR) described a set of tips for researchers interested in exploring the topic more systematically (Figure 5). Johnson commented on how infrequently researchers collect data on sex/gender, and argued that one needs to account for the appropriate sample size necessary to make comparisons between men and women. Moreover, she indicated that a range of definitions for gender exists, and underscored the need to become more precise in the usage of the term, “gender”.

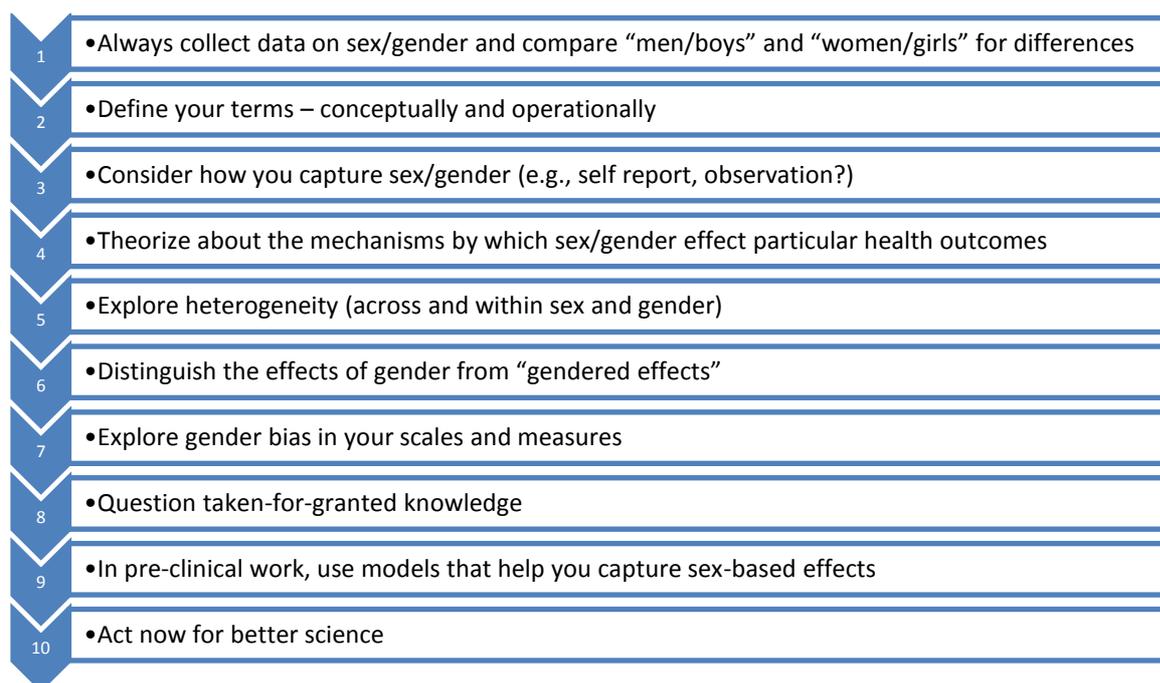


Figure 5

Importantly, researchers have to be cognizant of the potential gender bias in scales. For example, in the early days of the HIV epidemic, diagnostic criteria for AIDS were biased towards men, and consequently women were not being properly diagnosed. Johnson also commented on the need to think about innovative approaches to promote gender in research, as demonstrated by a research advocacy card developed by the IAS-ILF. From a policy standpoint, Johnson described the efforts of the CIHR to promote and conduct “research that meets the highest international scientific standards of excellence and ethics and that pertains to all aspects of health”. CIHR is a signatory of the Government of Canada’s Health Portfolio – Sex and Gender-Based Analysis Policy, as well as the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans. Both policies reflect why it is essential to integrate gender and sex into health research, as there is significant evidence to “demonstrate that biological, economic and social differences between women and men contribute to differences in health risks, health services use, health system interaction and health outcomes”.

Johnson also described how the CIHR has incorporated requirements for all grant applicants, with a set of questions they have to answer (Table 1). In addition, one helpful tool for applicants and peer reviewers is the

Bryan Baugh, medical director from Janssen, described his company's efforts in studying underrepresented populations, notably through the GRACE (Gender, Race and Clinical Experience) study⁶. GRACE was a Janssen-sponsored study examining darunavir/r-based therapy in treatment-experienced women in North America. Investigators recruited in areas of high HIV prevalence, specifically targeting clinical sites with significantly more female patients. GRACE was designed to investigate the role of race and gender, including socio-economic factors in treatment outcomes. Baugh noted that Janssen is committed to the study of ARV drugs in HIV-infected pregnant women, although he recognizes the inherent challenges in recruitment of this population. He also commented on how other companies are approaching Janssen to better understand how to maximize recruitment of women in trials.

Gina Brown is currently the Coordinator, Microbicides and Women and Girls Research in the Microbicide Trials Network, and based at the Office of AIDS Research (OAR), National Institutes of Health (US). Brown described how the OAR aims to ensure that HIV research priorities meet the needs of the epidemic, indicating that in 1991, the Office of Women's Health was established to address the health of American women by advancing and coordinating a comprehensive women's health agenda to address health care prevention and service delivery, research, public and health care professional education, and career advancement for women in the health professions and in scientific careers. The evolution of guidelines for requiring inclusion of women in NIH-funded research was an important turning point. Gina described how this has also trickled to basic science, but the guidelines are not specifically applied to tissues/cells.

As a journal editor, **Emma Veitch** spoke about transparency in reporting, which PLoS Medicine aims to cultivate. Veitch also raised the point about the extent to which one can generalize findings from studies in men to women, and advocated that gender should be incorporated earlier in study design to more robustly investigate the impact of sex/gender. She commented on how data sharing can be particularly important, as there are few individual patient meta-analyses in HIV clinical research.

Offering the perspective of a funder, **Rowena Johnston** stated that amfAR does not have an explicit gender policy as part of its grants programme. She noted the challenge of convincing biomedical researchers to incorporate sex/gender into their study designs, as these researchers are traditionally "reductionists". Notably, Johnston also touched on the issue of how MSM are easier to identify and recruit for clinical trials in the US than elsewhere.

Nass asked **Rahab Mwaniki** from Kenya to comment on the role of community in promoting gender in research. Mwaniki addressed the complex and multiple roles of women (that of mother, wife, caregiver), and how this becomes closely linked to the challenge of retaining women in clinical research in such regions as sub-Saharan Africa. She also emphasized that communities themselves need to have better information on why a

⁶ Falcon R, Bridge DA, Currier J, Squires K, Hagins D, Schaible D, Ryan R, Mrus J; GRACE Study Group. Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the gender, race and clinical experience study. *J Womens Health (Larchmt)*. 2011 Jul;20(7):1043-50. Epub 2011 Jun 10.

given trial seeking to recruit women has merit. Mwaniki's comments were echoed by a clinician in the audience from the University of South Florida, noting that randomized clinical trials are designed with a scientific rigour that does not account for the complicated lives of female participants. Bekker endorsed the concept of a paradigm shift in the way clinical research has been conducted to think about the social circumstances of women. She offered the example where her team installed a laundry machine in their clinical trial site to support women enrolled in their study, and called for innovative ways to think about recruitment.

Nass commented on a recent publication in JAMA by Jagsi and colleagues that reported gender differences in salary among physician researchers in the US, with male gender being associated with a higher salary⁷. This discrepancy partially reflects the continued struggle for women to have a voice, even in the halls of academic research institutions. In closing, there was a parting sense that a "brain shift" is necessary by researchers, coupled with a response by funders and a need to increase awareness among editors. Collectively, a gender-sensitive approach can minimize the burden of HIV in both men and women.

⁷ Reshma Jagsi, MD, DPhil, Kent A Griffith, MS, Abigail Stewart, PhD, Dana Sambuco, MPPA, Rochelle DeCastro, MS, Peter A Ubel, MD. Gender Differences in the Salaries of Physician Researchers. JAMA. 2012; 307(22):2410-2417.

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 ILF 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>.

Contact information:

International AIDS Society
Industry Liaison Forum
Avenue de France 23
CH-1202
Geneva, Switzerland
ilf@iasociety.org