

INTERNATIONAL AIDS SOCIETY INDUSTRY LIAISON FORUM (IAS-ILF)

FEBRUARY 2006
DENVER, USA

SCIENTIFIC AND INVESTMENT CONSIDERATIONS FOR RESEARCH ON PRE-EXPOSURE PROPHYLAXIS (PREP)

SUMMARY OF IAS-ILF MEETING

attendees

Joep Lange, University of Amsterdam, the Netherlands (IAS-ILF Co-Chair)
Michel Kazatchkine, Ambassador for HIV/AIDS, France (IAS-ILF Co-Chair)
Elly Katabira, Makerere University, Uganda (IAS-ILF Co-Chair)
Yasmin Halima, IAS-ILF, Switzerland/UK (IAS-ILF Co-ordinator)
Jacqueline van Tongeren, IAS-ILF, Netherlands (Meeting Organiser)

Keith Alcorn, Department for International Development, UK
Charles Boucher, University of Utrecht, the Netherlands
Pedro Cahn, Fundación Huesped and IAS, Argentina
Rob Camp, Treatment Action Group, USA
Ben Cheng, Collaborative Forum for HIV Research, USA
Myron Cohen, University of North Carolina, USA
Ernest Ekong, Military Reference Hospital, Nigeria
Mary Fanning, NIH, USA
Thomas Fischer, Boehringer-Ingelheim, Germany
Bob Grant, University of California San Francisco, USA
Cate Hankins, UNAIDS, Switzerland
Nick Hellmann, Gates Foundation, USA
Angela Kashuba, University of North Carolina, USA
Rodney Kort, IAS, Switzerland
Edde Loeliger, GSK, UK
Scott McAllister, BMS, USA
Craig McClure, IAS, Switzerland
Isaac Malonza, International Partnership for Microbicides, USA
Louise Martin-Carpenter, GSK, USA
Doug Mayers, BI, USA
Veronica Miller, Collaborative Forum for HIV Research, USA
Jeremy Nuttall, International Partnership for Microbicides, USA
Richard Ogden, Pfizer, USA
Praphan Phanupak, HIV-NAT and Red Cross Hospital, Thailand
Renee Ridzon, Gates Foundation, USA
Malte Schutz, Roche, USA
Wendy Snowden, GSK, USA
Jean-Marc Steens, GSK, UK
Paul Stoffels, Tibotec, Belgium
Randy Tressler, Pfizer, USA
Remko van Leeuwen, IATEC, the Netherlands
Eric Warren, Pfizer, USA

IAS INDUSTRY LIAISON FORUM, 5 FEBRUARY 2006, DENVER MEETING SUMMARY

1. Introduction

Joep Lange from the Academic Medical Centre in Amsterdam and Co-Chair of IAS-ILF opened the meeting by welcoming delegates and thanking speakers for their contribution. Yasmin Halima, Coordinator of IAS-ILF set the context by reminding participants that whilst pre-exposure prophylaxis (PREP) was the priority focus for ILF, this was not at the exclusion of other areas of interest for ILF. She confirmed that diagnostic monitoring - scaling-up of laboratory resources, rather than development of low-cost technologies and improving pharmacovigilance systems to monitor the safety and utility of antiretroviral treatments in developing countries were areas of research that had been identified by ILF members and the ILF advisory group. Future meetings would seek to address these issues.

The following represents a summary of the presentations and subsequent discussion that took place at the meeting.

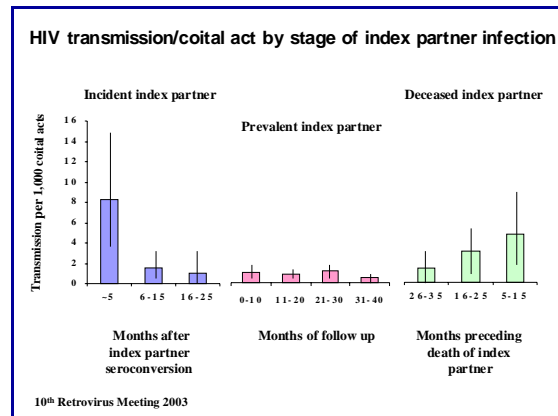
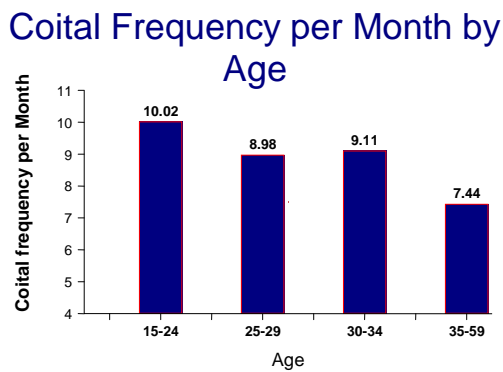
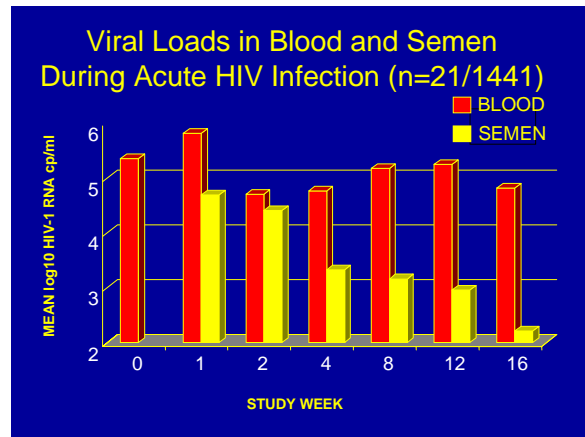
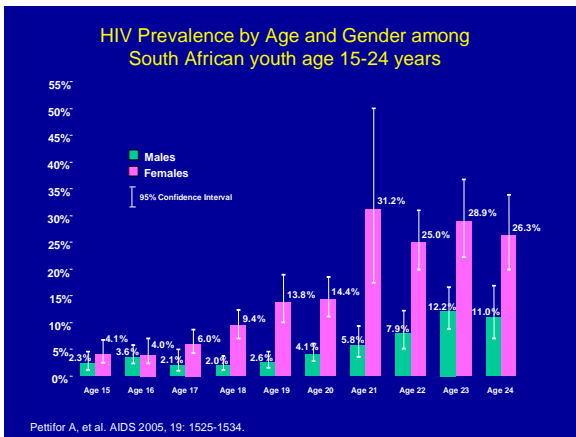
2. Scientific Considerations for PREP Research

Myron Cohen, Director of the Division of Infectious Diseases and HIV Prevention Trials Unit at the University of North Carolina, Chapel Hill presented an epidemiological overview correlating use of potential PREP with the trends in HIV population transmission. He described the epidemic spread of HIV as the result of the efficiency of transmission (a biological event), with duration of infectiousness multiplied by the number of people or partners exposed ($R_0 = bDC$).

Myron's presentation began with the biology of HIV transmission outlining the physiological determinants that enable or impede infection. He stressed that future PREP research will be influenced by some key questions which currently remain unresolved:

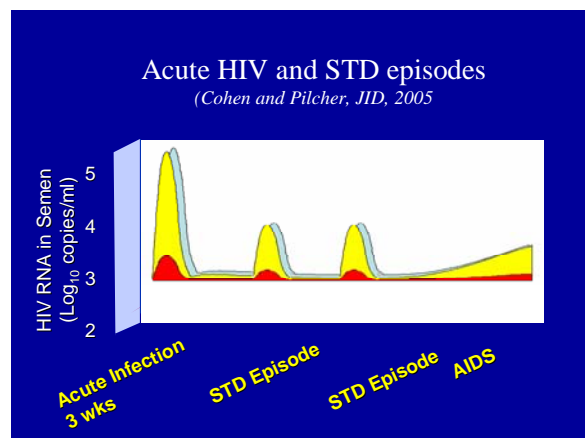
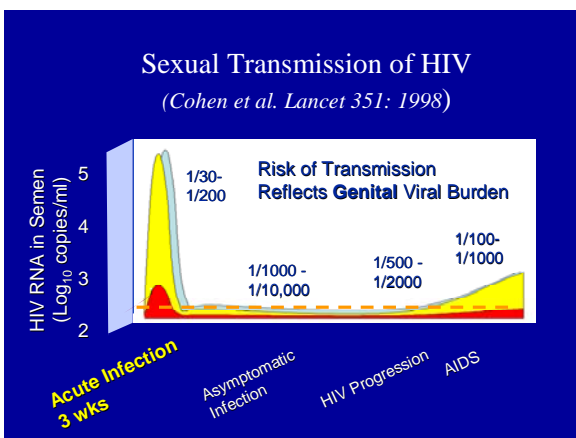
- is HIV transmitted by cell-free or cellular virus?
- why is the NSI (non-synctia inducing) variant preferentially transmitted?
- are all clades transmitted with equal efficiency?
- do women and men experience a different viral "bottleneck"?
- do all mucosal transmission events result in HIV?
- are transmitted variants unique in their genotype, envelope structure, and susceptibility to neutralizing antibodies?
- does antiviral susceptibility affect transmission?

Although our current understanding of the HIV pandemic is that it is preferentially driven by high-risk behaviours, namely men who have sex with men (MSM) who engage in frequent high-risk sexual encounters, injecting drug users (IDUs) and commercial sex workers, Myron questions whether this can adequately explain the magnitude of HIV spread in the developing world. A more plausible proposition is that HIV infection is most efficiently spread by the routine but unsafe, sexual activity of young people in areas of high prevalence; the spread of the epidemic in the young he stressed cannot be ascribed to promiscuity. Astonishingly he observes that in some high prevalence populations, the possibility of transmission following sex with a HIV positive individual could be as high as 100%! Findings from studies in South Africa confirm differences in HIV prevalence between young men and women, which may be explained by a number of factors including cultural, sexual practices and the increased biological vulnerability of young women to the acquisition of HIV. It also substantiates the assumption that the locus of infection is fuelled by sexual transmission during the primary stage of HIV infection.



The chronology of HIV transmission is marked by a phased sequence affected by changes in level of infectiousness. HIV transmission is amplified in early and late stage HIV disease. It is clear that these subjects drive the epidemic, with a low level of continued transmission occurring during the asymptomatic or chronic stage of HIV.

A further determinant in the potential to transmit HIV is the impact of episodes of sexually transmitted diseases with a concurrent increase in genital tract viral burden. Sexually transmitted diseases facilitate HIV transmission and large numbers of subjects with acute HIV infection present with STDs. This has largely been confirmed by studies that correlate viral loads in both blood and semen compartments.

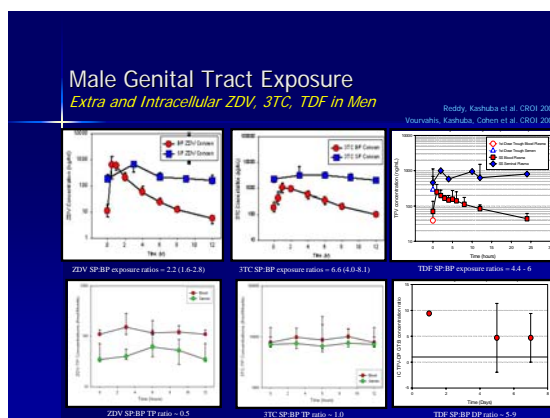
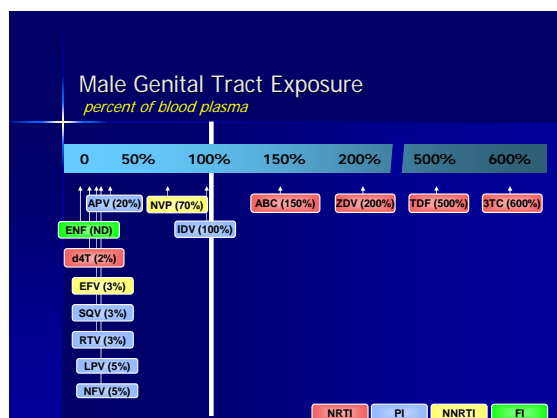


Finally, Myron concluded that to achieve the greatest impact, HIV prevention will need to increasingly focus on the groups most vulnerable to infection and emphasise the biological and

behavioral interventions that will need to be developed to reduce probability of HIV transmission.

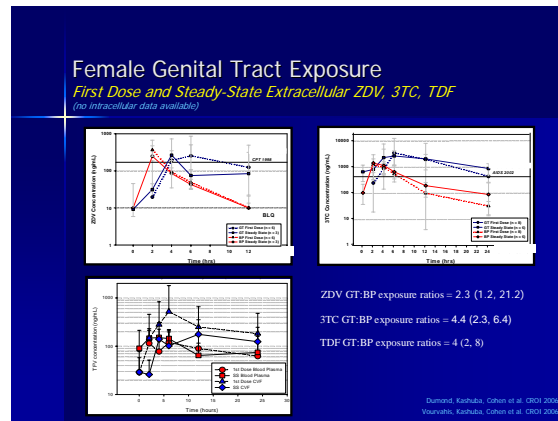
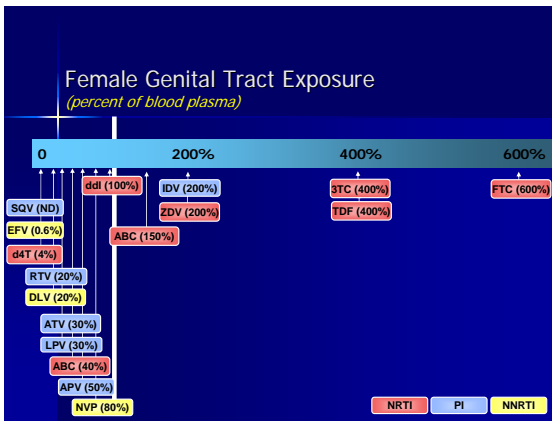
In response to Myron's contention that "not all drugs are created equal", Angela Kashuba, Associate Professor of Pharmacy at the University of North Carolina provided an illuminating discussion on antiretroviral pharmacology. She profiled drugs based on extracellular and intracellular genital tract exposure relative to blood plasma, followed by a review of the impact of different treatments on RNA in patients with established infection.

Angela began with the assertion that the combination/s of antiretroviral therapies that may optimally suppress or eliminate HIV from the genital tract remain unknown. But she noted that drugs that achieve higher concentrations in the genital tract may be best suited to the purpose of PREP referring to studies that have correlated effectiveness of treatment with drug concentrations in blood plasma. Although unreliable pharmacology data can be generated from research limited to single, random sampling in the genital tract, she asserted that full genital tract pharmacokinetic profiles can be generated for men and women using minimally invasive techniques. Using these novel methods, she has found that even with high plasma concentrations, the corresponding genital tract concentrations of highly protein bound drugs such as protease inhibitors and non-nucleosides remain remarkably low. This profile is significantly different for NRTIs which accumulate in genital secretions. For these drugs, however, intracellular triphosphate concentrations must also be evaluated as exposure might be lower than (e.g. zidovudine/ZDV), similar to (e.g. lamivudine/3TC), or higher than (e.g. tenofovir/TDF) concentrations found in peripheral blood mononuclear cells (PBMCs). Interestingly, genital tract concentrations achieved after administration of the first dose of antiretrovirals are not significantly different from concentrations achieved at steady-state; and in some cases may be higher.

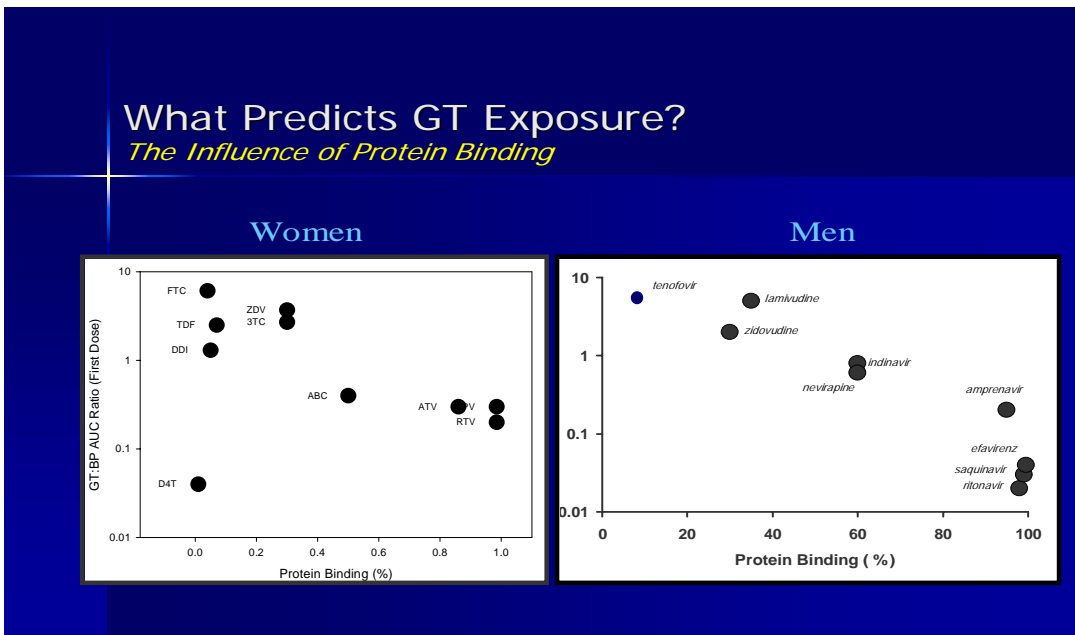


male genital tract exposure

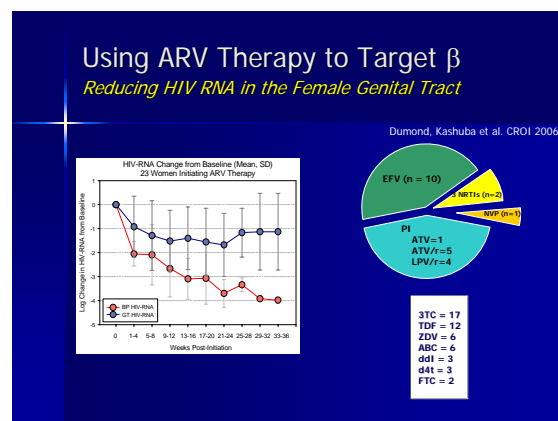
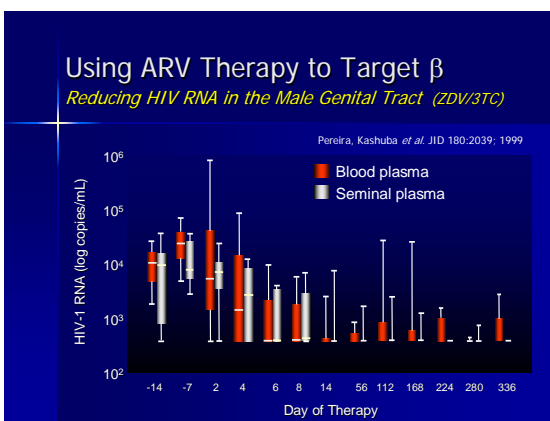
Generally, the relative extent of drug penetration into the genital tract is similar between men and women. Overall, high or low penetration of drug into the genital tract is directly related to the amount of protein binding these drugs exhibit: highly protein bound drugs achieve low concentrations in the genital tract, while less protein bound drugs achieve greater concentrations in the genital tract.



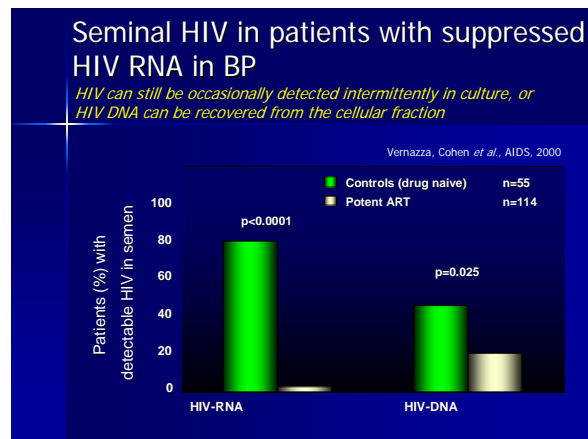
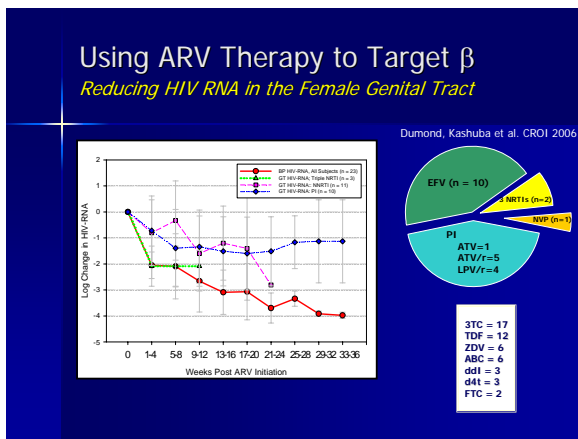
female genital tract exposure



predictors of genital tract exposure



ARV therapy to reduce RNA in male and female genital tract



seminal and cervicovaginal HIV in patients with suppressed BP RNA

Angela closed by outlining areas of development that need further focus including whether the monitoring of total parent drug as a correlate to actual drug concentration is adequate, defining protein-bound from free drug concentrations and if genital tract fluid concentrations are predictive of genital tract tissue absorption.. She noted the role of drug transporters and the need to understand whether up-regulation of transporters expression occurs inside the genital tract and what impact this has on drug concentrations. Angela confirmed that the pharmacologic aim in PREP research should be to develop drugs that accumulate in high concentrations in cells and genital compartments in order to improve the barrier to infection. Angela concluded by speculating on which drugs or combination of drugs may be more effective in preventing infection, including the role of agents that work extracellularly such as fusion and entry inhibitors.

3. Investment Considerations for PREP Research

Jim Rooney, Vice President of Clinical Research at Gilead Sciences gave an insightful account of Gilead's experience of working closely with the TDF PREP trials sponsored by the US National Institutes of Health (NIH), US Centers for Disease Control and Prevention (CDC) and Family Health International (FHI) with support from the Bill and Melinda Gates Foundation. Jim highlighted the considerations for selecting first or second-generation compounds for PREP: agents that can demonstrate potency, durability, simplicity of administration, good resistance and safety profile. He provided an algorithm for selecting future compounds and drug combinations, outlining TDF and FTC as a possible candidates. This matrix included potency, activity against target cells implicated in primary infection, ideally a long intracellular half-life, ease of dosing, high genetic barrier to delay resistance, long term safety and animal challenge data to support human clinical trials.

While there is a clear need for new prevention strategies such as PREP in the developing world, the need or use of PREP in developed countries, he asserted, is still not clear. PREP, he felt may be currently viewed by companies as an extension of post-exposure prophylaxis (PEP) and prevention of mother to child transmission (PMTCT) with studies conducted in small populations, with no regulatory labeling and its use guided by public health recommendations. In addition, labeling of proven PREP agents may require liability protection in the US (as with vaccines).

It is anticipated that first generation PREP studies will establish a point estimate for both safety and efficacy of the initial interventions, second generation PREP studies will build on these initial estimates to increase efficacy and safety. If the first tranche of PREP studies are effective, second generation studies are likely to use the effective arm as a control.

Jim noted that second generation studies are likely to include evaluation of:

- new agents: this may require evidence of safety and efficacy for treatment of HIV first
- combination therapy
- less frequent dosing: dependent upon PK of agents studied

- intermittent dosing: pre-/post-exposure therapy, anticipating or responding to high risk exposure (may be more appropriate in the developed world)
- comparison of systemic versus topical PREP
- use of 'effective' PREP arms as control

As Gilead has direct experience of PREP research from the current TDF PREP trials and as target for the controversies associated with these trials, Jim shared some key lessons learned by Gilead. The sponsor-company relationship and the company activist relationship he noted are important component in developing world prevention research and will continue to influence investments made by pharmaceutical companies on future PREP research. With the caveat that there may not be a huge number of companies keen to sponsor PREP studies in the developing world, nevertheless, he noted:

- the importance of partnering with groups who have expertise in clinical trials in the developing world, are interested in prevention research, and have their own source of funding
- that a third party group (usually a government or academic research group) is often the regulatory 'sponsor' for the study and responsible for clinical trial design, study execution, regulatory and safety reporting, data management, and analysis of study results
- that whilst Gilead provides study drug under a Clinical Trials Agreement, can comment on study design issues, will be copied on safety and regulatory communications and has access to data when results are available, they do not have final decision authority

The issue of activist intervention with its dramatic consequences on the initial PREP trials has had a profound impact not only Gilead, but other companies interested in PREP research. Jim accepted that responsibilities for the breakdown in communication lay with all the stakeholders including Gilead, but primarily, he felt that it should be the responsibility of study sponsors to ensure effective communication is maintained with local and international advocates as part of the research strategy. It was important however to note that the concerns from activists were not necessarily drug specific or even a dissent to PREP itself, but related to standards of care and access to medical resources in developing world settings. Jim concluded his presentation by stressing that in the future Gilead will assume a more active role in working with the sponsors to assure that community concerns are understood and addressed before, during, and after each study.

Mary Fanning, the Director of the Transition Office of International Research Integration at the Division of AIDS, NIH and Renee Ridzon, Senior Program Officer at the Gates Foundation both provided illuminating insights on the process of decision-making and considerations for future investment in future PREP research. In particular, Mary clarified that whilst NIH can indicate areas of interest for research, they rely on investigators approaching them with proposals for study. She outlined the NIH/DAIDS clinical trials network re-competition for both the scientific direction and clinical trial sites and the DAIDS oversight of trials. Mary gave a summary of the current PREP trials sponsored by the NIH including the Peru MSM study and a separate grant to study viral set-point and immune function in seroconverters in this and other trials. Whilst NIH policy does not permit purchasing of drugs for post-trial care, the NIH are keen to pursue research in countries where PEPFAR and Global Funds may be available to resource post-trial treatment. A great deal of commitment is being made to define and promote sound ethical and best practice based on their learning from existing trials. She noted that whilst none of these were new issues, the learning related to PREP had been particularly challenging. Mary commended the leadership role played by the Gates Foundation in addressing these challenges head-on. She also noted the importance of organisations such as the IAS in sustaining stakeholder dialogue.

Renee reinforced the experience of the Gates Foundation as similar to that of NIH as detailed by Mary. She spoke directly of the need and positive impact of the dialogue that had been so successfully initiated with international activists including Act-Up Paris. Renee stressed the immense value of humanising the process of communication between stakeholders by building

mutual understanding and supportive relationships in order to overcome misunderstandings and invest in shared goals. As well as addressing pressing ethical challenges, Renee gave remarkable insights into the technical challenges of PREP research. For example, she noted the high pregnancy rates found in these trials, as high as 20% at some sites, with serious consequences for maintaining study power. She did clarify that these pregnancies may be the result of using highly sensitive tests that are capable of detecting pregnancy very early, a proportion of which would not even be noted by women as they would be lost prior to a missed menses. However, given the safety, ethical and legal complexities, these were the tests mandated for use in these trials. She stressed the challenge of monitoring incidence in trials which actively look to prevent infection with use of prophylactic agents and prevention tools. For this reason, the sponsors with the support of IAS are coordinating a dedicated meeting with statisticians to identify and address these quantitative challenges.

Renee supported Jim's concern that sponsors need to play an active role in informing and maintaining effective communication with the community, both local and international. She concluded by thanking the IAS for its constructive role in facilitating and supporting the ongoing stakeholder dialogue first initiated in Seattle last year.

4. Summary Discussion

Intriguingly, Michel Kazatchkine, the French Ambassador for HIV and Co-Chair of ILF, prefaced the discussion by observing that we should recognise PREP as a 'South to North request'. This implies that PREP is urgent and mandates the coordination of responsible agencies connecting researchers and sponsors in the North to investigators in the South. Michel questioned the role of 'third-party' agencies extending responsibilities beyond sponsors and funders to share the broader policy and delivery with other 'effector agencies'. The concern for securing PREP once proven effective was supported by Bob Grant, from the University of California San Francisco who questioned that if developing countries were not able to purchase antiretroviral treatments, were they in fact able to afford PREP?

Bob also reinforced Myron's assertion that 'who is driving the epidemic' is of significance and should influence the design and location of future PREP research. Myron added that by identifying those in acute infection, we can further locate others who may have been exposed to HIV – the network transmission theory. Craig McClure, IAS Executive Director reinforced the issue of the strong correlation made between sexually transmitted infections and HIV, and asked Myron whether efforts are being made to scale up treatments for STDs and HPV vaccine (for example). Myron confirmed that the London School of Hygiene and Tropical Medicine is conducting studies in developing countries including a paediatric initiative involving the use of HPV vaccines.

From a scientific perspective, Elly Katabira from Makerere University and Co-Chair of ILF asked at what level of efficacy for PREP can be defined as 'effective'. In response, Mary Fanning from NIH confirmed that while these were not formally established values, the NIH are considering the utility of adding additional compounds to test if adding another drug may improve efficacy. Joep Lange lamented the lack of consistency in generating animal models used for the testing of (TDF) PREP, making any cross-study analyses currently impossible.

The meeting was closed by Joep Lange with thanks to participants, speakers and organisers.

The next full meeting of the IAS-ILF will be a dedicated satellite at the IAS conference on Sunday, 13 August 2006 in Toronto.

Note: the discussion outlined here reflects a summary of the information and analysis presented by speakers and participants and does not imply endorsement by IAS-ILF.