IAS INDUSTRY LIAISON FORUM (IAS-ILF)
25 FEBRUARY 2007, LOS ANGELES, USA

DEFINING INDUSTRY RESPONSIBILITIES IN PRE-EXPOSURE PROPHYLAXIS (PREP) RESEARCH AND IMPLEMENTATION

SUMMARY OF IAS-ILF MEETING

attendees

Joep Lange, University of Amsterdam, the Netherlands (IAS-ILF Co-Chair)
Elly Katabira, Makerere University, Uganda (IAS-ILF Co-Chair)
Rodney Kort, IAS, Switzerland (IAS, Senior Manger, Initiatives)
Yasmin Halima, IAS-ILF, Switzerland/US (IAS-ILF Coordinator)
Jacqueline van Tongeren, IAS-ILF, Netherlands (IAS, Meeting Support)

Nilda Altamirano, Impacta, Peru
Sally Blower, University of California Los Angeles, USA
Pedro Cahn, Fundación Huesped and IAS, Argentina
Rob Camp, Treatment Action Group, USA
Myron Cohen, University of North Carolina, USA
Rob Dintruff, Abbott, USA
Ernest Ekong, Military Reference Hospital, Nigeria
Steve Felstead, Pfizer, USA
Thomas Fischer, Boehringer-Ingelheim, Germany
Pedro Goicochea, Impacta, Peru
Bob Grant, University of California San Francisco, USA
Nick Hellmann, Gates Foundation, USA
Ann Kolokathis, BM, USA
Tumie Komanyane, Youth Health Organisation, Botswana
Edde Loeliger, GSK, UK
Karen Manson, Tibotec, Belgium
Louise Martin-Carpenter, GSK, USA
Veronica Miller, Collaborative Forum for HIV Research, USA
Julio Montaner, BC Centre for Excellence, Canada
Supatra Nacapew, Centre for AIDS Rights, Thailand
Na-Ri Oh, Boehringer-Ingelheim Germany
Wim Parys, Tibotec, USA
Lynn Paxton, CDC, USA
Praphan Phanuphak, HIV-NAT and Red Cross Hospital, Thailand
Renee Ridzon, Bill & Melinda Gates Foundation, USA
Jim Rooney, Gilead, USA
Zeda Rosenberg, International Partnership for Microbicides, USA
Paul Schaper, Abbott, USA
Andy Schmeltz, Pfizer, USA
Jean-Marc Steens, GSK, UK
Randy Tressler, Pfizer, USA
Remko van Leeuwan, IATEC, the Netherlands
Mitchell Warren, AIDS Vaccine Advocacy Coalition (AVAC)

Apologies: Michel Kazatchkine, Ambassador for HIV/AIDS, France (IAS-ILF Co-Chair)

Elly Katabira welcomed participants and provided an update from the ILF Advisory Group Meeting including ILF's focus on pharmacovigilance and expediting access to drugs in low-income countries. Elly introduced Zeda Rosenberg from the International Partnership for Microbicides (IPM).

Zeda Rosenberg, IPM

Microbicide development

Zeda described how research on microbicides has forged ahead since microbicides are less technically challenging than vaccines. She emphasised that the production planning takes place at the same as research planning.

Community and advocacy history

Zeda explained some of the history of microbicide development in particular, that the affected community identified the need for female-controlled prevention modalities. In this respect, ethical and acceptance issues in the community were discussed early on in the research process. Community Advisory Boards (CABs) worked closely with local advocate groups on issues of informed consent and compensation. CABs are provided with regular updates on trial development.

Research issues

IPM has prioritized its activities in countries with a high HIV incidence in women. An important consideration in biomedical prevention trials is the prevention tools and counseling that trials are ethically obligated to provide, reducing HIV transmission rates and incidence. Trials therefore need to consider the impact that provision of prevention tools make on study incidence and increase cohort size accordingly to compensate. IPM is also developing a care package for workers at the trial sites. IPM SOC guidelines framework: (i) reflects general principles, (ii) acknowledges that standardisation across countries and trial sites may not be feasible, (iii) is flexible to accommodate changing environments and the need to adapt to meet unique local circumstances and (iv) is meant to be updated regularly (e.g., responding to results from the male circumcision trials).

In particular, the IPM SOC Guidelines include guidance on:

- Community engagement
  - commitment to participation of local communities prior to, during, and after clinical trials
  - community advisory process
  - regular updates and end of study meeting

- Informed Consent
  - commitment to ensuring that participants have freely given informed consent
  - ongoing process
  - appropriate compensation

- HIV risk-reduction
  - counseling
  - provision of male and female condoms

- STI diagnosis and treatment

- Referral for individuals who test HIV-positive at screening
  - post-test counseling and psychosocial support
  - referral agreements in place

- Provision of ARVs for trial participants
  - appropriate therapy and care
  - initiation based on host country/WHO guidelines
  - choice of therapy based on viral phenotype and drugs licensed in host country

- Services for study staff
  - PEP for HIV and HBV
  - appropriate ARVs if HIV-infected through trial-related activities
  - workers' compensation coverage

- Treatment and compensation for physical harm
  - medical treatment for adverse reaction or injury
  - compensation for illness or injury resulting from the study

- Post-trial access
  - partnership with donors and host country to make an effective, licensed product available to study participants

Partnerships with industry and government; development, regulatory

IPM Product Development Partnerships (PDP) define agreements between IPM, industry and local government. Industry provides technical, scientific and financial support and help to find trial sites; discussions regarding access to proven compounds start early. The Guiding Principles for PDP include: (i) reduced time to licensure, (ii) provision of resources for infrastructural and financial support, (iii) collaboration with both public and private sector partners and (iv) maintaining open dialogue with communities.

Zeda described the license structure. IPM retains development rights and receives a license that is royalty-free, has no up-front payment, is for distribution on an affordable basis and covers resource-poor countries. Zeda mentioned that regulatory agreements have been negotiated with the European Medicines Evaluation Agency (EMEA) and other regulators.

IPM has acquired non-exclusive royalty-free licenses to develop, manufacture and distribute antiviral compounds as microbicides in developing countries from several major drug companies including:

- TMC 120: NNRTI licensed from Tibotec
- M167: CCR5 blocker licensed from Merck
- BMS793: gp 120 binder licensed from Bristol-Myers Squibb
- PMPA: NRTI, joint IPM/CONRAD licensed from Gilead

Implementation

IPM's commitment to planning for implementation and delivery starts with research design. Zeda noted the many lessons learned from industry included how companies are able to market the same product simultaneously to different groups. IPM ensures that strategies for implementation are flexible enough to respond to different country circumstances. Implementation issues addressed in the policy include health insurance schemes and compensation for trial participants who seroconvert or experience drug-related harm.

IPM Standard of Care document

The IPM Standard of Care (SOC) guidance reflects the need to be flexible, and preempt a range of possible circumstances. 60% of women screened for IPM trials test positive for HIV. IPM guidance includes referral strategies for treatment and post-test counseling. Provision for seroconverters is dependent on treatment available in the country where the study is undertaken. (IPM document available on IPM website)

Yasmin Halima, ILF PREP Discussion Paper

Background and references

The discussion paper is based on a synthesis of discussions from scientific, activist and consultative forums as well as supplementary interviews with ILF members. The paper is intended as a reference and stimulus for discussion, with the intention that the input from this consultation and future inputs will result in a guidance document for release at the 4th International Conference on HIV Pathogenesis, Treatment and Prevention in Sydney, 22-25 July 2007. IAS in collaboration with AVAC is meeting with advocates on the evening of 25 February 2007 to discuss PREP research issues in anticipation of future meeting. This is a continuation of the work that the IAS has undertaken on behalf of the Bill & Melinda Gates Foundation.

Yasmin reiterated that bioethical frameworks are historical documents and reflect priorities of the time and circumstances in which they were developed. Many do not address detailed issues of harm and compensation in prevention trials. Many of the references included in the ILF discussion document are extrapolated from vaccine and microbicides including the IPM SOC framework.

Industry responsibilities

Industry responsibilities were discussed whether in the role of direct sponsors or supporters of PREP research. The planned ILF guidance document is not intended to protect companies from any potential liabilities but rather to establish clear delineation of areas of responsibility and consensus. The aim is to promote further industry interest and investments in PREP research by developing consensus on respective role and responsibilities between industry and other stakeholders in the biomedical prevention field.

Key issues covered

- compensation to trial participants for harm caused by study drug
- prevention tools provided during the study
- provisions for those diagnosed with HIV at screening
- provisions for those who seroconvert during the study
- implementation and delivery policies if drug is proven effective
- engagement with community advocates and civil society

Summary of group discussion

Ethics or operating standards? Role of IRBs

Many participants felt that some of the concerns raised including SOC and compensation were not necessarily ethical nature but reflected the need to precisely define and apply standards. One member noted that problems have arisen in trials even where the standards for treatment were agreed by IRBs. This raised the issue of the role of IRBs needing training on treatment, prevention and ethical issues to ensure that issues do not arise retrospectively.

Group members than explored some pertinent issues that are yet to be resolved:
- SOC for post-exposure prophylaxis (PEP) for needle-stick injuries to staff
- treatment for other infections identified at recruitment including HCV and HBV
- provision of antiretroviral treatment to staff at trial sites
- defining minimum standard operating procedures (SOP) for IRBs
- independent, ongoing training on ethics for IRBs and ethical review boards
- role of UN agencies in the setting of practice guidelines

Challenging AIDS exceptionalism. Are we setting the bar too high?

The discussion on HIV-exceptionalism was animated with several members agreeing that we should be careful about setting exceptional standards whereas others felt that HIV did raise some unique ethical, social and clinical challenges. The emerging consensus reflected in the IAS discussion document and reiterated at the meeting was that seroconversions that occur during the course of the study should not be the responsibility of study sponsors. The case was made that in non-infectious diseases we do not make sponsors liable for illnesses contracted during the trial period. Some members felt strongly that it is impractical to agree HIV treatment that would only be indicated many years into the future and that we should be careful not to set unrealistic, undeliverable standards, thereby endangering future research.

It was also noted that treatment activists who had engaged with PREP research over the past couple of years have demanded higher standards for compensation. One member questioned whether we may be confusing bioethics with social justice; are researchers and advocates concerned with protecting autonomy in the North and promoting social justice in the South, he asked.

Research related issues: liability, compensation and screening out

A participant from the NIH confirmed that treatment for adverse events are now permissible in studies undertaken by the NIH. However, several people noted that for many sponsor sites there are not viable insurance schemes and little clarity on liabilities or responsibilities. It was also noted by many that local governments should bear some responsibility for these additional burdens including improved provision for HIV treatment.

It was noted that the numbers of those screened out for pre-existing HIV is potentially very high. One donor noted that referral mechanisms for those screened out are not currently working and that we urgently need 'buy in' from the community to define adequate standards and strategies to address this issue. She added that we may need to accept that SOC may need to be set higher. It was also confirmed that similar issues had been confronted in the vaccine field and policies developed for example by IAVI as a requirement but that none have been put to test.

Country preparedness

There was a distinct consensus amongst the participants that countries must be prepared to treat those who are diagnosed at screening or who seroconvert during the trial. Countries need to be prepared with 'standard' agreed regimens for treatment. One possibility is to target support from WHO specifically for implementation. Sponsors expressed the need for "readiness to participate" lists that identify which countries and sites have good SOC. One investigator however asked if we should only consider countries that are 'ready'; if we do, newer countries may be left out of the research process.

Industry and research

A number of key questions were put to industry:

- how does a company decide which products should move forward in prevention research?
- when are products in development considered for research as potential agents for PREP?
- how much safety data is needed for a new class?

Gilead responded that they make compounds available by Phase II for oral administration whilst Pfizer noted that they recently established the safety profile of their CCR5 compound which is currently in Phase IIb now. Pfizer noted that the experience with other CCR5s had made them more hesitant but they were willing to explore maraviroc as a potential PREP agent. GSK confirmed that it has offered several products for PREP research. The representative from GSK added that the company believes in assuming total responsibility for the research and development process and not handing it over to another party. Tibotec however noted their position as quite different; they are willing to consider requests for testing compounds by agencies committed to prevention in developing countries. It was noted that originator companies have different strategies and responses to issues of ownership, partnership and development.

Press

The role of effective communication and specific issues of engaging the press was raised by participants. Zeda reported that IPM has developed a Microbicide Media Communication Initiative which defines strategies for communication, reporting and disaster planning. Such initiatives, she added, help to counter misinformation when that occurs.

Community involvement and training

A community advocate from the South noted that since PREP research is targeted at high-risk populations, greater support strategies are needed to safeguard their rights including the need for 'rights-based' and not just research related training. In working with IDUs, she noted does the emphasis need to be on stopping drug use first?

Another advocate also from a resource-limited country stressed the urgent need for training CAB members; without effective understanding CAB members run the risk of being tokenistic representatives. Training should not only address trial issues but advocacy skills are needed as well including for example, how to share technical information with the public or potential trial participants. She observed that it was not always clear to CAB members what information was confidential and which could be shared.

The Chairs thanked participants for their contribution. Yasmin confirmed that the next ILF meeting will be held in conjunction with the IAS conference in Sydney and will be a satellite session on the challenges of PREP implementation and delivery. Dates and programme will be circulated.

Yasmin Halima, 5 April 2007