



INTERNATIONAL AIDS SOCIETY
INDUSTRY LIAISON FORUM

DISCUSSION PAPER

**BUILDING CONSENSUS ON INDUSTRY RESPONSIBILITIES RELATED
TO PREP RESEARCH AND IMPLEMENTATION**

**ILF Stakeholder Meeting
10:15AM – 12:30PM**

**San Gabriel Room A & B
Westin Bonaventure Hotel
404 South Figueroa Street
Los Angeles, CA, USA
25 February 2007**

Introduction

Pre-exposure prophylaxis (PREP) involving the use of antiretrovirals demonstrates great potential for reducing HIV transmission. Efficacy data from animal studies and safety outcomes from recent clinical trials have established PREP as a leading candidate for HIV prevention research. In recognising this potential, IAS has been engaged with developments in PREP through scientific debates, sustaining a high-profile informed policy and media response at international AIDS conferences and convening regular multi-stakeholder consultations. Controversies related to the conduct of clinical trials testing tenofovir disoproxil (TDF) have had a major impact on PREP research leading to misunderstanding, misrepresentation and in some cases, premature closure of trials. The controversies partly resulted from inadequacies in guidance from existing international ethical frameworks that failed to designate with sufficient specificity the role and responsibilities of the various stakeholders involved in clinical trials. Biomedical prevention trials have also presented investigators and donors with unique challenges including the size of cohort trials required to ensure sufficient study power and ethical considerations involved with risk reduction counselling.

This paper seeks to address some of these limitations by:

- providing a summary of issues that frame the current challenges and consensus in PREP research gleaned from recent investigator, sponsor and community debates
- providing background references from available literature and discussions with ILF and non-ILF members from industry, community and research
- generating debate within the ILF, primarily with industry members and select non-industry representatives from academia, community, sponsor and donor groups

The comments included in the paper reflect contribution from a number of different sources including: (i) a synthesis of issues and consensus emerging from various stakeholder discussions, (ii) supplemented by individual interviews with ILF and non-ILF members (for the purposes of this discussion their names and agency affiliations have not been identified) and (iii) these have been supported by references to examples from available literature.

ILF will draft consensus guidance based on the outcome of these discussions that is acceptable to ILF industry members and leading non-industry stakeholders. The final document will be launched at the 4th IAS conference on HIV Pathogenesis, Treatment and

Prevention in Sydney, July 2007. Given the ILF emphasis on defining and supporting industry responsibilities, the focus of the exercise is to explore what are the responsibilities that can and should be assigned to industry as supporters or sponsors of PREP research as distinct from non-industry stakeholder responsibilities.

This paper is divided into four main sections.

1. General background highlighting the historical and contemporary context within which guidance on biomedical prevention research has emerged.
2. A reference list of ethical frameworks that state or imply guidance on issues pertinent to prevention and clinical research.
3. A more detailed discussion of areas of contention that has emerged from the discourse on prevention research with particular reference to the PREP trials currently underway.
4. Summary list of areas on which consensus needs to be developed.

1. OVERVIEW COMMENTS

1.1 It is worth bearing in mind that many of the guidance documents referenced here were developed in a particular historical context. In general, the utility of most guidelines are limited since they promulgate broad principles and recommendations for practice. They reflect an acceptable and practical consensus at the time in which they were developed and are influenced by the agenda of the organisations instrumental in shaping them. Moreover, very few bioethical frameworks make explicit reference to prevention research; we often infer guidance for conduct of biomedical prevention research from frameworks intended to safeguard patients involved in therapeutic trials.

1.2 It is also of note that many of the guiding documents were historically developed by physicians for physicians, including the Helsinki Declaration compiled under the auspices of the World Medical Association. As such, they concern themselves with medical ethics, i.e. safeguards for the individual largely enshrined in the patient-physician relationship rather than an emphasis on population, public health. We often find ourselves therefore, attempting to apply principles from medical bioethical frameworks in a way that was not historically intended. This also results from the fact that comparable ethical frameworks do not exist in public health. The late Jonathan Mann highlighted the absence of a robust ethical frameworks actively formulated by

the different disciplines in public health. (Medicine and Public Health, Ethics and Human Rights in Jonathan M Mann et al, Health and Human Rights: A Reader 1999)

- 1.3 In terms of the specific discussion here regarding sponsor responsibilities, it was clearly expressed by many that the responsibilities of sponsors towards subjects who participate in trials are contingent upon national and international regulations. Moreover, these may not vary substantially based upon population demography, whether it is a vaccine, microbicide or an oral drug that is being tested, or by type of sponsor, company versus government research organisation for example.
- 1.4 In many of the discussions, responsibilities were assigned to the sponsors of studies regardless of whether they were industry or not, i.e. greater responsibilities were not associated if the sponsor was a pharmaceutical company.
- 1.5 It is also important to distinguish between 'sponsorship' versus 'support'. Sponsorship that may involve the spectrum of operational responsibilities, i.e. funding the entire design, conduct and evaluation process versus the offer of drugs for testing by a company may lead to different expectations. As yet, the gradation of responsibility is unclear and remains at the heart of the debate.
- 1.6 Investigators and others recognise that there is an absence of a core group of community advocates who understand and coordinate community contribution and advocacy on PREP research.
- 1.7 Some issues paramount at the time of the controversies seemed to have become somewhat dissipated, whether this is because they have been resolved or simply forgotten is not clear. A clear example is the issue of providing independent risk counselling in prevention trials. Advocates including those from Cameroon expressed great concern on this issue suggesting that there is a conflict of interest for investigators in offering prevention counselling in a prevention trial. The consensus now appears to be that sponsors and not local providers should be responsible for training and delivery by independent counsellors. The emphasis is on ensuring quality and independence of counselling offered in prevention trials rather than who is providing the service.
- 1.8 A range of animal models have been developed to test PREP. Since they employ different design approaches to testing efficacy, meta-analyses across animal studies is not possible. However, this does not seem to be of significant concern to the scientific community. The emerging consensus seems to be that proof-of-concept studies in animals are useful before proceeding in human trials and the design of these will

depend on the drug, dose and transmission mode that is being tested. It may be that given how far the field has progressed there may not be a need for one, unified animal model that tests for efficacy of PREP but that multiple study designs could serve to inform future trial designs.

2. SUMMARY OF GUIDANCE ON REQUIREMENT FOR TREATMENT AND CARE FOR PARTICIPANT IN HIV PREVENTION TRIALS

- Declaration of Helsinki (2002)
 - No specific obligations regarding provision of medical treatment during research
 - Every patient should be assured of the best proven diagnostic and treatment methods

- CIOMS International Guidelines (2002)
 - Guideline 21: Ethical obligation of external sponsors to provide health-care services
 - External sponsors are ethically obliged to ensure the availability of treatment for subjects who suffer injury as a consequence of research interventions

- UNAIDS Guidance Document (2000)
 - Guidance Point 16: Care and treatment for HIV/AIDS...should be provided to participants... the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country

- Nuffield Council on Bioethics (2002)
 - ... conclude that when research into preventive measures is conducted... participants who develop the disease being studied should be offered a universal standard of care for the disease... Where it is not appropriate to offer a universal standard of care, the minimum... that should be offered is the best available intervention as part of the national public health system for that disease

- Universal Declaration on Bioethics and Human Rights, UNESCO General Conference, 33rd Session, 20 October 2005
 - Added the notion of *social responsibility*... and the creation of independent, multidisciplinary and pluralist ethics committees

- WHO Initiative for Vaccine Research reported at a meeting in Malawi entitled ethical considerations in relation to provision of care and treatment in vaccine trials ... access to treatment while “morally praiseworthy”, is not an ethical obligation and may provide additional obstacles to developers in conducting vaccine trials
- Guidelines for SOC for research on New HIV Prevention Technologies in Nigeria ... the standard of care and treatment given to participants in Nigeria be no less than the highest achievable standard that can be attained within the country – not necessarily limited to that presently obtainable within the national government health sector
- The MRC/DIFD Microbicides Development Programme (MDP) in 2003 Identified the Following Principles

Participants identified with medical conditions including STI and HIV at enrolment or during the study will receive diagnosis, assessment and referral appropriate to the local site

The principal investigator at the site will have to take responsibility for ensuring effective treatment for STI excluding HIV either through the project or referral to local services

MDP will not provide ART for participants in prevention trials, but the principal investigator at the site will assist, in the context of local settings, in identifying appropriate support and care

- Undue Inducement in Clinical Research in Developing Countries: Is It a Worry?
Ezekiel J Emanuel, Xolani E Currie, Allen Herman, Lancet, July 23 2005
 - differentiate "inducement" from "undue inducement"
 - differentiate "undue inducement" from "unfortunate circumstances"

The article concludes that providing antiretroviral medications as part of an otherwise ethical research trial in a developing country in which such medications are not generally available—or are available only on a restricted basis—does not constitute undue inducement

Offering antiretroviral drugs to HIV positive people is not an undue inducement causing poor judgment but an incentive reinforcing prudent judgment; offering

antiretroviral drugs as part of a research trial enhances rather than compromises autonomy

- Formalizing Protocols and Contracts to Capture Criteria for Standards Agreed
Researchers should formalize referral networks, ensure that the local services that trial participants are referred to have the capacity to provide needed services, and provide resources and capacity development to strengthen these services
 - Creating Effective Partnerships for HIV Prevention Trials, Report of a UNAIDS Consultation, Geneva 20-21st June 2005

3. SPECIFIC ISSUES THAT NEED CONSENSUS GUIDANCE

3.1 COMPENSATION FOR HARM CAUSED BY STUDY DRUG

General comment

There is little dissent on this issue with unanimous agreement that compensation should be made available for adverse events caused by study drug. In particular, the responsibility for compensation should rest with study sponsors including donors regardless of whether they are independent or industry. There was concern expressed over the NIH policy for not compensating for study drug related adverse events.

References

Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002) states that investigators have a responsibility to ensure participants have access to free medical treatment and “such financial or other assistance as would compensate them equitably” for injuries.

Ethical guidance based on a consultation held by WHO and UNAIDS (2004) *Treating people with intercurrent infection in HIV Prevention trials* calls on governments to amend their laws to ensure that trial participants are insured for coverage to address any trial-related harm.

The HIV Vaccine Trial Network *Participants’ Bill of Rights and Responsibilities* promises “treatment and payment of resulting medical costs” for physical injuries resulting from trial participation.

3.2 PROVIDING PREVENTION TOOLS FOR TRIAL PARTICIPANTS

General comment

There is general agreement on the principle that proven prevention methods should be made available at every trial site. However, there was recognition from the community and other stakeholders that it might not be possible to deliver all the prevention tools at every site. Community advocates felt that they wanted to see demonstrable efforts before accepting that it was acceptable not to have all prevention tools made available to trial participants. This is a matter that should be negotiated with both local and international activists. Advocates emphasised that not being able to provide all prevention technologies should not prevent a trial from going ahead.

References

The Global Campaign for Microbicides (GCM) consensus statement (2005) argues that “microbicides trials have a special obligation to attend to the sexual and reproductive health needs of participants, including offering direct provision of safe, appropriate contraception for trial participants.”

IPM guidelines (2006) confirm that “male and female condoms will be provided free of charge to trial participants at every study visit. IPM will either provide contraception counselling and contraceptives, or refer trial participants to appropriate family planning clinics in the community if they want contraception.”

3.3 TREATMENT FOR THOSE DIAGNOSED WITH HIV AT SCREENING

General comment

Study sponsors should at the very least provide CD4, viral load, and referral to local treatment provider. There is agreement that clinical sites should be established in countries where treatment is likely to be made available but that this should not be a prerequisite to establishing trial sites for PREP research. Community members felt that best efforts should be made to negotiate country level responsibilities prior to research.

References

IPM aims to “establish clinical sites in areas where there is capacity for delivery of antiretrovirals treatment to the broader community. IPM will work closely with sites and trial participants to facilitate effective referrals.”

Guidelines for SOC for research on *New HIV Prevention Technologies in Nigeria* (2005) asks investigators and sponsors to “ensure that identified HIV positive individuals who screen out...[are] ensured access into an *existing* care, treatment and support service.”

A multi-stakeholder consultation organised by IAS recommended that individuals who test HIV positive at intake be referred to the National AIDS program and that laboratory tests needed to qualify for the program be paid for by the research study. The group also recommended that trial volunteers be provided with PMTCT services, and treatment for Hepatitis B and Hepatitis C virus co-infection. *From IAS Stakeholder Consultation Report, Building collaboration to advance tenofovir research* (2005)

3.4 TREATMENT FOR SEROCONVERTERS

General comment

The debate here seems to be whether HIV acquisition should be considered a study-related harm. There is an emerging but not unanimous consensus that acquisition of HIV should not be perceived as a study-related harm. As such, industry and other non-industry investigators felt that they should not be responsible for treatment or compensation for those who seroconvert. This issue needs urgent resolve. Community advocates differed in their response. Some felt that compensation should be made, even if it were not treatment per se since this would not be indicated but that there should be some recompense. Other community members felt that if it was not a study related harm and so compensation was not due. At the very least there is agreement that CD4, viral load and resistance testing should be offered by study sponsors regardless of industry or non-industry status.

References

The references related to this issue mostly from the vaccine and microbicide field are complex and contradictory.

IAVI has pledged HIV care to participants who seroconvert and to make ARVs available to the participant for up to five years after ARV therapy is initiated. NIH HVTN has committed to providing ARVs and is creating a fund to support drug purchase... the question is how to guarantee appropriate care years after a particular trial has concluded in areas that have very limited health care infrastructure. “In the end, only

governments can provide long-term care guarantees. We need a development approach to strengthen their capacity to provide these services.”

Seth Berkley, IAVI Executive Director, quoted from IAS Stakeholder Consultation Report, *Building collaboration to advance tenofovir research* (2005)

Declaration of Helsinki requires neither compensation of research related injury nor treatment of those who become infected during an HIV prevention trial.

Global Campaign for Microbicides (GCM) consensus statement (2005) calls for ARVs to be provided to trial participants “based on ethical aspirations and existing social and political realities”.

IPM Guidelines for the Conduct of their trials note that participants who become infected with HIV during the course of a trial will be offered appropriate ARV therapy and HIV-related care. The threshold for initiation of ARV treatment will be determined with reference to the host country’s treatment guidelines or, if those guidelines are not in place, through guidelines established by the World Health Organisation (WHO). IPM will pay for appropriate ARV treatment until this treatment is available through national HIV treatment programmes or other sources ... each participant who becomes infected will be offered testing to determine whether the participant’s virus is susceptible to established first-line therapy. In the event that clinically relevant resistance is detected, the participant will have access to ARV treatment licensed in the country appropriate to her infection and related care.”

Guidelines for SOC for research on *New HIV Prevention Technologies in Nigeria* (2005) notes that “mechanism for ensuring access of HIV seroconverters during a prevention trial should be defined at the national level before the trial commences” and that “provision of ARV therapy should be for the lifetime of the trial participant who seroconvert. This should be packaged through a health insurance scheme for participants.”

UNAIDS *Ethical Consideration in HIV Preventative Vaccine Research* (2000), Guidance Point 9 states “HIV infection acquired during participation in an HIV preventative vaccine trial should not be considered an injury subject to compensation unless it is directly attributable to the vaccine itself or to direct contamination through research-related activities.” This position is endorsed by the Nuffield Council (2002) and has since been adopted by the MRC in South Africa in 2003.

James Childress from the Hastings Center (1976) analyses compensation of research-related injury based on the notion of positional risk, i.e. risks that would have not have

otherwise been encountered. It asks whether the injury would have been avoided if the injured party had not been in that position. If a research subject becomes infected due to administration of a vaccine contaminated with HIV or via contaminated needles then the harm of HIV infection is proximately caused by study participation and compensation is due. However, in most cases subjects in prevention trials will become infected because of their membership in a high-risk group and not because of trial participation. It recognises that since the trial participation is not the proximate cause of the harm there is no research-related injury and no basis for a claim of compensation.

The US Health Education and Welfare Secretary's Task Force on the Compensation of Injured Research Subjects (1977) describes research-related injury as: "harm, disability or death suffered by a subject at risk of biomedical and behavioural research ... where such injury is (1) proximately caused by such research and (2) on balance exceeds that reasonably associated with such illness from which the subject may be suffering ... at the time the subject began participation in the research." It asks whether the injury would have been avoided if the injured party had not taken part in the research

CIOMS *International Ethical Guidance for Biomedical research Involving Human Subjects* (2002), Article 19 states that "investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap .. the injury must be the result of the subjects' participation in the research."

Catherine Slack et al in *Provision of HIV Treatment in HIV Prevention Trials: A Developing Country Perspective* in *Social Science and Medicine* (2005) conclude that on the basis of current evidence it "is difficult to argue that as a general rule HIV infections in trials should be treated as though they are research-related and compensated by sponsor provision of high quality treatments.

R. Macklin in *Double Standards in Medical Research in Developing Countries* (2004) state that given the relatively small numbers of individuals who participate in "preventative HIV/AIDS vaccine trials, and the much smaller number that will become infected during the trial, it is .. a gross over-estimate to think that the cost of providing antiretroviral treatment to this group would be exorbitant. Informal estimates indicate that the cost would be affordable even if required for the lifetime of this group."

3.5 PROVISION OF PREVENTION DRUG IF PROVEN EFFECTIVE

General comments

There is agreement that if PREP is proven effective, the compound should be registered for use in the country that hosted the research – whether this should be under the indication of PREP or the expectation is that the drug will be used off-label is not clear. There is less consensus on whether the drug should be made available preferentially to trial participants. There is little mention by any of the stakeholders at present on implementation, scale-up or delivery of PREP to developing countries.

References

The updated Declaration of Helsinki (2002) states that “at the conclusion of the study, every patient entered in the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods.

The Global Campaign for Microbicides (GCM) consensus statement (2005) argues that trial participants should have preferential access to any test product this is shown effective and GCM encourages researchers and donors to “actively seek to access to the produce post-trial through .. negotiation with host country governments and product sponsors.”

3.6 COMMUNITY ADVOCACY

General comments

General agreement including those within industry that industry should take more responsibility for engaging with community advocates and supporting community developments in PREP research, even if they are not instrumental in sponsoring studies in PREP.

References

The NIH Department of AIDS (DAIDS) refer to their initiative on research preparedness calling for a broader community engagement beyond the trial community, “stakeholders in preparedness activities that address prevention research that are not linked to a particular trial.”

The Ministry of Health representative from Ghana at the IAS stakeholder consultation stressed that “community engagement...should be done in a culturally appropriate context and one that does not conflict with our systems of governance.”

UNAIDS in their consultation report (2005) entitled *Creating Effective Partnerships for HIV Prevention Trials* suggest developing “a matrix of audiences (including, but not limited to, donors, researchers, “community”) and timeframes for community engagement, and identify specific outcomes for the different audiences/perspectives.”

UNAIDS *Ethical Considerations in HIV Preventative Vaccine Research* Guidance Point 5 (2000) advises “to ensure the ethical and scientific quality of proposed research, its relevance to the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation and distribution of results of HIV vaccine research.”

Charles Weijer and Guy LeBlanc in *The Balm of Gilead: Is the provision of treatment to those who seroconvert in HIV prevention trials a matter of moral obligation or moral negotiation?* *Journal of Law Medicine and Ethics*, (Winter 2006) defines the longevity of community engagement “The community’s involvement in research extends from the inception of research through its publication.”

4. DEVELOPING CONSENSUS, MAKING DECISIONS

The purpose of the ILF discussion is to highlight some of the contentious issues in PREP research and articulate areas of agreement in addressing these. Given industry’s unique role in drug development and supply, ILF is keen to establish consensus on areas of industry responsibility and support for PREP research and delivery.

In summary, ILF is invited to consider decisions for the following:

4.1 Compensation for harm caused by study drug

Research regulations stipulate that study sponsors are required to compensate for drug-related harm caused during the course of the study. However, if a company only supplies drugs to an independent research agency for testing, should the responsibility still rest with the sponsor or the drug company to provide compensation for drug-related harm?

4.2 Providing prevention tools for trial participants

Provision of proven prevention methods must be made available to trials participants in prevention trials. But is it necessary to provide all prevention tools at every site as a prerequisite to study? And should trials not take place in countries where researchers cannot guarantee the necessary provision tools, e.g. sterile needles for studies involving injecting drug users? Should companies support trials in these circumstances?

4.3 Treatment for those diagnosed with HIV at screening

Consensus is needed in three key areas: (i) should study sponsors, regardless of industry or non-industry status, provide at the very least CD4, viral load, and referral to local treatment providers, (ii) must there be clinical infrastructure established in countries where PREP research is being planned, one that can prescribe antiretroviral therapy to those for whom treatment is indicated, and (iii) what efforts must be made to secure country-level agreements for treatment provision through national programmes prior to research? Should companies support trials in countries where treatment cannot be guaranteed for individuals screened out because of existing HIV infection?

4.4 Treatment for those who seroconvert during the course of the study

Should HIV acquisition be considered a study-related harm? The answer to this question is critical to determining whether sponsors of study are responsible for providing HIV therapy, regardless of their industry or non-industry status. Since HIV treatment is not indicated at time of infection, should seroconversion during a study mandate some financial or other compensation? Are the demands for compensation likely to be higher for industry sponsors or supporters of a study than those made of non-industry sponsors?

4.5 Provision of prevention drug if proven effective

This falls within the main key area of industry responsibility. If PREP is proven effective, will the compound be registered for use in the country that hosted the research? Will this be under a specific indication for PREP? Should the drug be made available preferentially to trial participants and who would decide this? Should companies work with host governments to ensure that policies are in place to secure efficient delivery of PREP?

4.6 Community advocacy

There is strong consensus amongst industry and the research and advocate community that industry should engage more actively with international and local advocates on PREP research and implementation. At present, very few companies have taken the initiative to develop a coherent dialogue and support community developments in PREP. The issue is

what precisely should industry be doing to engage community advocates in PREP research and policy discussions? How should they identify and support the most appropriate representatives for engagement?

Yasmin Halima, Coordinator, IAS-ILF. 5 February 2007