

MEETING REPORT:

**Consultation on HIV Treatment
in the Context of Prevention Trials**

February 28, 2003



Sponsored by
The Global Campaign for Microbicides
International AIDS Vaccine Initiative (IAVI)

Meeting report prepared by Emily Bass

Acknowledgements:

The Global Campaign for Microbicides and the International AIDS Vaccine Initiative would like to thank the meeting participants and Emily Bass for her skill at capturing a rich and complex discussion. In addition we would like to acknowledge the editing and layout assistance of Imogen Fua and Anna Forbes of the Global Campaign at PATH.

This meeting and publication was funded by US Agency for International Development (USAID) to the Global Campaign for Microbicides, through the HealthTech IV Cooperative Agreement # GPH-A-00-01-0005-00 managed by PATH. The opinions expressed herein are those of meeting participants and do not necessarily reflect the views of USAID.

The Global Campaign for Microbicides is a broad-based, international effort to build support among policymakers, opinion leaders, and the general public for increased investment into microbicides and other user-controlled prevention methods. Through advocacy, policy analysis, and social science research, the Campaign works to accelerate product development, facilitate widespread access and use, and protect the needs and interests of users, especially women. The Global Campaign's secretariat is housed at the Program for Appropriate Technology in Health (PATH).

The International AIDS Vaccine Initiative is a global organization working to speed the development and distribution of preventive AIDS vaccines—the world's best hope for ending the AIDS epidemic. IAVI's work focuses on four areas: mobilizing support through advocacy and education; accelerating scientific progress; encouraging industrial participation in AIDS vaccine development; and assuring global access.

For questions or additional copies of the report, please contact:

The Global Campaign for Microbicides
c/o PATH
1800 K Street NW, Suite 800
Washington, DC 20006
E-mail: info@global-campaign.org
Tel: 202 822 0033
Fax: 202 457-1466

International AIDS Vaccine Initiative
c/o National AIDS Trust
New City Cloisters
196 Old Street
London EC1V 9FR
United Kingdom
Tel: +44 (0) 20 7216-0078
Fax: +44 (0) 20 7216-0111



TABLE OF CONTENTS

A.	Introduction.....	3
B.	The Ethical Backdrop for Standard of Care (SOC) Decisions.....	3
C.	Reports from the Field (1): Ethics in the Real World.....	6
D.	Reports from the Field (2): Preparing for Scale Up.....	8
E.	Status of Current Network Deliberations.....	9
	I. HIV Prevention Trials Network (HPTN).....	9
	II. International AIDS Vaccine Initiative (IAVI).....	9
	III. Microbicides Development Programme (MDP).....	10
	IV. HIV Vaccine Trials Network (HVTN).....	11
	V. Contraceptive Research and Development Program (CONRAD)	12
	VI. Walter Reed Army Institute of Research (WRAIR).....	12
	VII. Division of AIDS (DAIDS, NIH).....	12
F.	Common Themes.....	13
G.	Open Questions.....	14
H.	Conclusion.....	17

A. Introduction

On February 28 2003, a diverse group of researchers, clinicians, ethicists and advocates met for a consultation on HIV treatment in the context of prevention trials, co-organized by the Global Campaign for Microbicides and the International AIDS Vaccine Initiative (IAVI), and co-facilitated by Lori Heise, Director of the Global Campaign, and Saul Walker, Policy Advisor for IAVI.

Several factors prompted this meeting. Global access to highly active antiretroviral therapy (ART) for HIV-infected adults and children is increasing, as is provision of antiretrovirals (ARVs) to prevent mother to child transmission of HIV. The costs associated with these medicines are dropping. New funding streams, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) are helping to put ARVs within reach of more countries where sophisticated AIDS treatment has historically been considered unfeasible.

At the same time, microbicides and vaccines are moving from small-scale Phase I trials to larger, community-based efficacy and effectiveness trials, which will screen and enroll thousands of volunteers. The majority of these trials will take place in resource-poor settings where provision of ART exists on a pilot basis, if at all.

Against this backdrop, those involved in HIV prevention trials, including studies of vaccines, microbicides and behavioral interventions, have focused increased attention on the type of care offered to trial participants, their families and their communities, particularly HIV-positive individuals within these groups.

Key questions include: What constitutes an acceptable basic package of care to be provided to individuals who become HIV-positive during the course of a prevention trial? Should this care also be made available to participants' family members and the wider community? Do trial sponsors have an obligation to provide ART to any or all of these groups? If so, does the obligation extend beyond the duration of the trial? Who should be expected to pay for care once a trial is finished?

The meeting was designed as a forum for open discussion of these complex issues. The goal of the meeting was to identify issues and points of agreement and disagreement, not to build consensus or to generate a single standard for all trials. Instead, the meeting sought to facilitate sharing across the major UK and US research networks of the ongoing discussions happening within networks and between communities and research partners in resource poor settings.

B. The Ethical Backdrop for Standard of Care (SOC) Decisions

National Institutes of Health (NIH) ethicist, Reider Lei, discussed current international ethics guidelines and the questions they engender in his talk, "Ethical Reasoning and ART Treatment: Insights from NIH Consultations on Exploitation and Fair Benefits."

As Lei detailed, several documents, including the Helsinki Declaration, the Council for International Organizations of Medical Science (CIOMS) guidelines, the National Bioethics Advisory Committee (NBAC), and the UNAIDS guidance on ethical conduct of vaccine trials, provide ethical guidelines for the conduct of research. However, none of these documents provides clear guidance on the standard of care for individuals who acquire HIV during HIV prevention trials.

One reason for this omission is that prevention trials enroll volunteers who are not HIV-infected. According to current guidelines, the obligation to these healthy individuals can be met through provision of a high-quality package of counseling and prevention services designed to ensure that they remain HIV-negative.

While no explicit statements in these documents address the trial sponsor's responsibility for volunteers infected during trial, some of the guidelines do mention this scenario. The 2002 CIOMS guidelines state that provision of treatment for such diseases is "morally praiseworthy" but not necessary, and recommends that decisions be made in consultation with the host country and communities where research will occur. The UNAIDS guidelines on vaccine trials state that sponsors should seek "at minimum" to ensure access to the "best attainable" care available in a given country. The Helsinki Declaration does not address whether or not researchers have an obligation to provide treatment for a disease contracted during the course of a trial.

Lie observed that two key questions have emerged as particularly germane to multi-site international research networks:

- **Is it ethical to allow different levels of care depending on different economic conditions in settings where research takes place?**

All guidelines except for the Helsinki Declaration specify conditions for "allowable" differences in standard of care (SOC) in different settings, (including NBAC, the Nuffield Council, CIOMS, and UNAIDS). This opens the door for trials to take place in developing countries under conditions that would not be allowed in the industrialized world. While controversial, prohibiting any departure from a "uniform" standard could paradoxically increase the potential for exploitation by mandating study procedures that make it less likely that the findings will be relevant to the local population.

- **Should "reasonable availability" be a condition for protocol approvals?**

It has been suggested that trial sites be selected on the basis of availability of a minimum standard of care in the surrounding community and that sites in which such care does not exist should be considered ineligible. Such a requirement would bypass some of the issues in the SOC debate; however, it has the major drawback of potentially excluding many regions from research.

These questions and related topics generated a broad-ranging discussion and several recurring themes were brought up and debated throughout the day by participants. They are summarized below.

Key Discussion Points:

- **A strict medical ethics framework may actually call for *less* comprehensive SOC's during and after trials than those currently being developed by trial designers.**

"It is important to state that, while arguments can be made from a policy point of view [to provide ART], there is no ethical imperative to provide antiretroviral treatment," said Lei. He stressed, however, that this view derives from a strict medical ethics framework, and does not incorporate the various political, economic and social realities that also contribute to SOC decisions. Nevertheless, prevention trials that do not provide ART are not, by definition, *unethical* according to the medical ethics framework laid out in existing guidelines.

- **There are ethical ambiguities around provision of ART for volunteers *only*.**

Calling it, “a defect in the guidelines as such,” Lei noted that the current guidelines address obligations to trial participants *only*. They do not address obligations to communities writ large. This issue held great significance for many meeting participants, who were troubled at the prospect of providing a disproportionately elevated standard of care to select members of a community. In addition to creating disparities in locally available care, such an approach could also lead to drug sharing within families, if only a single family member is eligible for medication. Many participants felt, however, that such issues should not be used to justify the decision to deny care to trial participants altogether. Strategies including home visits, directly observed therapy and other interventions can be used to increase the likelihood that volunteers will take their medications as prescribed.

- **The standards described as “best available” and “highest attainable” in ethical documents remain difficult to define, and subject to divergent interpretation.**

Noting the “notorious difficulty in understanding what “highest attainable” means,” Lie highlighted an unresolved distinction between what is attainable in the context of a trial and what is attainable in a country over all. There is also often a wide divergence between what national policy documents cite as the domestic “standard of care” and what services or care may actually be available locally.

- **The requirement to ensure post-trial availability is ambiguous vis a vis obligation to trial volunteer versus community.**

According to Lei, existing guidelines do not provide clear direction on the ethical obligations regarding post-trial accessibility, particularly to communities as opposed to individual volunteers. He reported that availability to the general community is addressed “most strongly” in the CIOMS guidelines, which state: “The sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to the inhabitants of the underdeveloped community in which the research was carried out. Exceptions to this general requirement should be justified . . .”

Participants discussed the fact that making drugs ‘reasonably available’ after the trial is only one way to ensure “fair benefits” to individuals and communities who participate in trials. In addition to privileging one type of benefit, this standard frequently cannot be guaranteed. If the test products prove to be ineffective or if it is not approved for distribution by the host country’s national regulatory authorities, the trial sponsors can’t fulfill the commitment to make the test product available to communities in which it was tested. Lori Heise further noted that efforts to ensure “reasonable availability” of drug or product post trial should not preclude consideration of community input into preferred benefits for trial participation.

- **There may be a conflict between research ethics and medical ethics or the “ethics of care.”**

Participants felt that there was a tension between the ethics that guide health providers and the ethics that guide researchers. They pointed out that, while SOC policies may make distinctions between the two professions on paper, trial investigators often experience a reality that blurs their identity as care provider and researcher. While research ethics may specify a certain level of care, local health care professionals may feel an obligation to provide more to the individuals and families with whom they work and live. Conversely, an elevated standard of care for volunteers-only may conform to ethical norms of research, but may nevertheless be interpreted as undue inducement by community members or providers.

- **Communities may perceive concrete benefits to participating in research even in cases where the direct relevance of the research to the community is questionable.**

The example was given of a trial of the antimalarial drug Malarone, which was tested in a resource-poor setting even though the costly drug was targeted at wealthy travelers. The community said that they wanted to participate in the trial nonetheless, since it would bring them 2 years of state-of-the-art care that would not have existed otherwise.

C. Reports from the Field (1): Ethics in the Real World

“As we take elegantly designed studies into the field, that’s where reality hits. What we find is the existing standard of care is minimal – average health care expenditures in many countries is less than \$5 per annum – so not much is being provided. If you are doing research in that setting, then you have to improve conditions. Anything that you offer is substantially more than what is [available] in these countries.”

— *Quarraisha Abdool Karim, CAPRISA, University of Natal*

Irving Hoffman (University of North Carolina, Chapel Hill), reviewed SOC decisions made in the context of several studies funded by the HIV Prevention Trials Network (HPTN).

Speaking generally, Hoffman observed that over the past several years, the health care infrastructure has deteriorated in Malawi, the site for several of the trials he discussed. The result of this deterioration is a widening gap between trial site care and national health care offerings. Another trend is the increasing number of HIV-infected individuals progressing to symptomatic disease stage.

Citing specific examples, Hoffman described several HPTN studies conducted over the past three to five years. HPTN 024, for example, enrolled 3500 HIV positive pregnant women at four African sites into a Phase III study of treatment of asymptomatic chorioamnionitis to reduce the risk of MTCT. All women received short-course nevirapine (NVP) for prevention of MTCT of HIV, and trial participants were randomized to receive antibiotics or placebo during the second trimester and during labor.

This trial was designed and approved prior to the Durban 2000 International AIDS Conference, which many participants at the consultation referred to as a turning point in discussions of ART in the developing world. “There was never any discussion of ART treatment for the mothers,” Hoffman said. “It was not on anybody’s radar screen. Internally, we asked ourselves, ‘What can we do?’ The standard of care in Malawi is so poor, and the trial is so big, and, (at that time), the price of ART was so high that to provide ART to study participants seemed inconceivable.”

The median CD4 count among women enrolled was 330, lower than the average in women enrolled in the original Uganda-based NVP trial, HIVNET 012. This, Hoffman noted, meant that the women enrolled in HPTN 024 were sicker, had higher viral loads, and were more likely to transmit HIV to their infants than those on HPTN 012, regardless of the intervention. Despite the NVP treatment provided, 17% of the babies born to HIV-positive mothers in 024 were HIV infected at 4-6 weeks, a larger percentage than that seen in the 012

trial. “As a result of this, with no budgeting for care, we had 40-50 nonscheduled visits per day for HIV symptoms in mothers and babies.”

To deal with this, the HPTN site in Malawi used research monies to set up a separate clinic to meet participants’ needs. Hoffman noted that this clinic provided, “slightly higher” than national standard of care during trial, but no care after the trial. Although all the women exiting the trial were referred to a local, dedicated HIV clinic, no provision of ARV care was assured.

Hoffman then turned to an upcoming trial, HPTN 035, a Phase IIB four-arm microbicide trial that will enroll 3100 HIV negative women in STD and family planning clinics. As Hoffman noted, voluntarily HIV counseling and testing (VCT) is considered SOC in most developing countries but is “not specifically” available in all of the clinics where the 035 trial will enroll participants. As a result, the trial planners are conducting an audit of existing VCT services at the different sites to identify missing pieces, prior to the study launch.

The HPTN 035 planning process has raised other issues, common to many trials, including:

- Whether or not participants will have access to the product should it prove efficacious; if so, at what (if any) cost, and for how long?
- Is the study responsible to the women who are identified as being HIV positive during pre-trial screening and, as a result, excluded from trial participation?
- Who should shoulder the financial, technical and administrative responsibility for care offered to participants once the study has concluded? The host country? Host research institution? Primary funder? Pharmaceutical company or product developer? Other interested parties such as USAID?

Finally, Hoffman outlined the design process for HPTN 052, a study that will enroll HIV infected individuals in serodiscordant relationships and their HIV-negative partners. HPTN 052 will look at whether or not ART reduces rates of sexual transmission. HIV-positive individuals will be randomized to receive immediate treatment, or treatment based on CD4 count and clinical diagnosis, and rates of transmission to partners will be compared in both arms.

The trial will have 60 months of follow up. The HPTN has partnered with the AIDS Clinical Trial Group (ACTG) to enable many of the HIV positive individuals who do not meet the study criteria for enrollment in 052 (i.e. those with CD4 counts below 200 at time of screening) to be enrolled in an ACTG-sponsored ART trial instead. “We are attempting to set up a safety net [for excluded HIV positive individuals],” said Hoffman.

Key Points:

- **All research takes place within a changing landscape; the realities of local and national health care capacity may be getting worse, instead of better.**
- **Care needs *during* the trial will vary with enrollment criteria.**
- **ARVs are not the only “missing piece” in SOC. Other services, like VCT, treatment for STDs and TB prophylaxis, may also be lacking.**
- **Treatment modalities will change over the course of long-term trials: state of the art care in 2003 will not be the same in 2010.**

D. Reports from the Field (2): Preparing for Scale-Up

Faced with the prospect of providing improved care for a segment of the population (i.e. trial volunteers), research entities are increasingly talking about helping “scale-up” treatment services for the population at large through financial and technical support.

Paul Weidle of the US Centers for Disease Control and Prevention (CDC) described the scale-up process as it has taken place in the Kibera slums in Nairobi, Kenya. The CDC is currently working in collaboration with several Kenyan groups on an operations research project that will scale up “from scratch” to ART provision in Kibera.

Weidle cited the following as options currently available to research entities seeking to provide treatment to communities:

- Refer to the government program if one exists, and the government agrees (in Thailand, for example, the Bangkok Metropolitan Authority provided ART for breakthrough infections during the VaxGen trial);
- Purchase or subcontract services, possibly from the private sector (the US embassy, for example, has an agreement with The Aga Khan Hospital, a private Kenyan hospital, to provide care to its HIV-positive employees and dependents);
- Buy into business-run health care programs – such as those run by multinational mining companies, banks, or other large companies;
- Buy into donor-supported projects; and
- Build health care delivery capacity from scratch.

The CDC has taken the “from scratch” approach in Kibera, where it partners with the African Medical and Research Foundation (AMREF), KICOSHEP, a community-based NGO, the Kenyan Ministry of Health (MOH), and the Kenyan Medical Research Institute (KEMRI). The MOH will develop and evaluate standardized treatment algorithms, monitoring strategies and training programs and KICOSHEP will provide home based care workers that provide a link back to the clinic and provide follow up for patients receiving care. AMREF will provide screening and care that involves TB treatment, OI prophylaxis, and ART at a basic clinic built in Kibera in 1999.

The CDC will provide funds for drugs, laboratory tests, diagnostics, and provide the technical expertise for development and evaluation of the program based on the principle of a simplified and standardized approach to care. The ART drugs will consist of the following first and second line regimens:

- A) stavudine, lamivudine, nevirapine
- B) zidovudine, didanosine, lopinavir/ritonavir

Lab monitoring will include an annual viral load and CD4, and a complete blood count and AST¹ four times per year as basic parameters for toxicity evaluation. The cost of this package is approximately \$1500-2000/person/year, including ARVs.

E. Status of Current Network Deliberations

I. HIV Prevention Trials Network (HPTN)

Quarraisha Abdool Karim (CAPRISA, University of Natal) reviewed the deliberations over SOC that have taken place at the HPTN, noting that, “We live in world of great inequities, where differences between North and South are growing day by day.” She also observed that each HPTN subject area—PMTCT, STIs, microbicides, behavior and ART—“brings its own challenges.”

The HPTN’s “fundamental, proactive approach” is to “leave research participants and communities better off than had research not taken place.” There is no standard policy requiring provision of antiretroviral therapies or any other intervention to trial participants. Decisions about the form that these improvements take are made in consultation with volunteers and their communities. This strategy reflects the belief that an approach based on “the centrality of the research participant” alone can create a “two-tiered society where one group—i.e. research participants—gets everything that is available in the North and the other group—non volunteers—gets nothing.” Implementation of overall improvements through progressively improving care, on the other hand, can be sustained beyond the lifespan of the study or trial.

Abdool Karim pointed out that many communities where HIV prevention work is being carried out are “getting sicker and sicker” as people with HIV progress to the symptomatic disease stage. Given this, she said, “We have to acknowledge that prevention and care are a continuum.”

She concluded by reflecting on how thinking at the NIH is “evolving” towards viewing its various trials networks as a part of this continuum. In an ideal scenario, someone in a prevention trial who acquires HIV during the course of the study would be enrolled in a study of recent seroconverters. Thus, upon reaching the point where guidelines recommend treatment, he or she could be enrolled in an AIDS Clinical Trial Group (ACTG) or Pediatric AIDS Clinical Trials Group (PACTG) trial of antiretroviral therapy. A version of this approach is being applied in the case of HPTN 052, a study that seeks to enroll 1700 serodiscordant couples, to study the effects of treatment on HIV transmission. HIV-positive people with CD4 counts of less than 300 are excluded from the trial at screening but are offered the opportunity to enroll into an ACTG treatment trial.

“There is merit in this approach,” Abdool Karim concluded, which goes beyond drugs or making drugs available. It’s about staff, training, and referral systems, and about looking at how research sites can serve as bridging sites for wider access. Research provides some opportunity for addressing key issues around preparing for scale up.”

II. International AIDS Vaccine Initiative (IAVI)

Saul Walker presented the draft SOC developed by IAVI for Phase III vaccine trials. The current document states that IAVI will ensure that all trial participants have access to high-quality primary care and HIV prevention services for the duration of the trial. IAVI will also ensure that participants who become HIV infected have access to treatment, care and support, including ART when clinically indicated. Individuals found to be HIV positive during the screening process will be referred to local services.

Because individuals who seroconvert during the course of a trial are unlikely to require treatment during the course of the trial, IAVI proposes to set aside funds through a locally-managed account (i.e. with a health insurance company) that would pay for 5 years of antiretroviral treatment once the start of treatment is indicated. This money could be placed in a government-run trust fund for HIV positive vaccine trial participants (e.g. South Africa).

Like the HPTN, IAVI will “try to use its investments to improve primary health care more generally” and will “actively seek to use investments in trial infrastructure, training and local services to leverage support for improvements in healthcare and HIV-related services for communities in which trials take place.” This advocacy work will be done with the goal of securing treatment and care for dependents and family members, who would not be directly covered by IAVI’s current SOC policy.

III. Microbicides Development Programme (MDP)

Sheena McCormack (Medical Research Council, UK) summarized discussions within MDP, which has seven potential African trial sites. The grant started in 2002 and at the first Investigator’s Workshop, the group discussed the principles of practice for the research to be conducted within the program. Regarding SOC, the Investigators reached consensus on the following:

- Participants identified with medical conditions including sexually transmitted infections (STIs) and HIV at enrollment or during the study will receive diagnosis, assessment and referral appropriate to the local site.
- Principal Investigators (PIs) at each site will take responsibility for ensuring effective treatment for STIs *excluding* HIV either through the project or referral.
- MDP will not provide ARVs for participants, but the PI will assist in identifying appropriate support and care in the context of the local setting.

It was agreed that the program should continue to debate these issues especially as national policies evolve and guidelines are developed in other research areas (e.g. HIV vaccine trials).

McCormack said that these consensus points had been discussed subsequently within their working and decision-making groups, and recently reconfirmed. The Investigators were concerned about providing treatment in an environment in which it was not otherwise available, because doing so creates inequity in the community and potentially constitutes coercion to enroll in the trial. She noted that this had not yet been discussed formally within the MDP’s recently established community working group. McCormack also noted that the Investigators were comfortable with differences in care between MDP sites, given the diversity of care offered on a community-wide basis across the sites.

In several sites, the community’s primary concern was about access to HIV testing services. MDP has found it necessary to establish VCT services, in some instances for both men and women, in several communities. “This issue has been a key issue for our program,” McCormack said. “VCT may be in national policy

documents but the service is not accessible to communities in many of our study sites, and the stigma of being found positive with nowhere to be referred is the first issue to address.”

McCormack said that the MDP would be revisiting these issues in on-going discussions.

IV. HIV Vaccine Trials Network (HVTN)

Connie Celum (University of Washington) presented the policy on follow-up and ART treatment for breakthrough infections in HVTN trials. The HVTN approach is “to treat those who breakthrough, not those who are diagnosed during the screening process, because the volunteers are the ones who have taken the risk of participating in a trial of an experimental HIV vaccine.” The HVTN is also committed to working with outside partners to provide services to individuals excluded during the screening process.

Celum also explained a distinction that the HVTN has made between early and late phase trials. In Phase I/II trials, provision of ARVs is “not a scientific issue, it is an access issue,” Celum said. A natural history protocol, HVTN 403, has been designed to follow individuals infected during early phase trials for the purpose of obtaining preliminary data on the effect of vaccine-induced immune response on the natural history of early HIV infection.

The HVTN 403 protocol does not provide a standardized approach to antiretroviral treatment because only about 50-60 breakthrough infections are expected to occur during this Phase I-II trial. This anticipated sample size is too small to measure accurately the differences in viral and immunologic natural history between vaccines and placebo recipients. The HVTN intends to establish a fund to provide ART to volunteers who seroconvert during the HVTN phase I-II trials at international sites where treatments are otherwise inaccessible.

ART provision in the context of Phase III trials has important scientific implications in terms of evaluating vaccines that may lower viral load or delay disease progression, rather than completely blocking infection. In this context, “a uniform protocol for ART provision is desirable and can be embedded in parent vaccine protocol or a separate ART protocol for breakthrough infections,” Celum said.

The desire to learn as much as possible about vaccine effects on viral load, CD4 trajectory, and time for ART initiation engenders substantial scientific interest among vaccine developers in documenting when and how ART is accessed by volunteers with breakthrough infections. One way to capture these data are to enroll volunteers who became HIV-infected after enrollment into a standardized ART protocol, in which they are monitored without treatment until CD4 or viral load thresholds indicate that treatment should be initiated. This approach would help to identify factors that need to be assessed to determine the effect of vaccine-induced immune response on the magnitude and durability of viral suppression; the potential for viral escape; subtype and phenotype of infecting viral strains; and differences in early HIV natural history related to age, race or gender.

“We need to get more input from international sites and ethicists about the issue of coercion around offering ART; and about whether to handle treatment as a separate protocol or not,” Celum said. The HVTN plans to offer basic information on availability of treatment for breakthrough infections during the initial consent process of vaccine trials. Looking ahead, Celum said, “We need to continue to discuss the duration of ART, including financing and provision of care. Most people feel that if we are going to do this, we need to do it for life.” In this and other discussions, meeting participants observed that strategies could be devised whereby trial sponsors assume responsibility for ART provision throughout a finite time period, rather than making a lifetime

commitment. This would have to be done with the understanding that other entities, including national and NGO programs, would assume responsibility at the end of the interval of trial-sponsored care.

V. Contraceptive Research and Development Program (CONRAD)

Lut Van Damme reviewed SOC decisions made by the reproductive health research organization, CONRAD. She reported that CONRAD's policy is to discuss with local investigators, the SOC that should be provided to trial volunteers who seroconvert. CONRAD, she added, "will try to put funds into some kind of mechanism so that volunteers will be able to access the locally defined SOC for a certain length of time during (if necessary) and after the trial." CONRAD also provides treatment for curable STIs diagnosed during screening and follow up. It does not, however, provide ART to individuals who test positive during screening for trials.

VI. Walter Reed Army Institute of Research (WRAIR)

Col. Deborah Birx reviewed the policy at the Walter Reed Army Institute of Research, a program funded by the US. WRAIR has determined that "care and treatment need to be at the community level and not the individual level" and has committed to providing the same level of care to trial volunteers and community members, especially in rural Africa where field sites are integrated into the community. "I know that if we give ARVs or Septra, to one volunteer, these pills will be broken 3 and 4 ways, or given to a son on one day, a daughter on another day. There is no way in rural Africa to deliver ARVs to individuals, especially women, without treating families."

Birx noted that WRAIR is less restricted than NIH-funded research programs, which are prohibited from using grant funds to improve infrastructure (by building a clinic, for example). "In many places, there will be no clinic," Birx pointed out, and WRAIR has been able to build facilities that serve research initiatives, the volunteers and the community at large.

The components of this care include a full prevention platform, with VCT, condoms, counseling and provision of antiretroviral to prevent mother to child transmission (PMTCT) of HIV. She noted that, when PMTCT services were introduced, site uptake of VCT rose from 50% to more than 90%.

For those who become HIV-infected during the course of a Phase III vaccine trial, WRAIR has set the goal of providing both antiretroviral therapy and OI management, and facilitating social support. At present, WRAIR is conducting operational research to gather information about the impact of ART, launching two operational research trials in Tanzania and Kenya. This inquiry will include a cost-effectiveness analysis done at a Kenyan tea plantation and a Tanzania-based study comparing generic antiretrovirals with brand name drugs. The owners of the tea plantation approached WRAIR about conducting the study. "There is a lot of interest in treating and evaluating worker productivity," Birx noted.

VII. Division of AIDS (DAIDS), NIH

Mary Fanning (DAIDS) described past and ongoing deliberations at the Division of AIDS, which funds research in the US and internationally. At present, DAIDS requires trial sponsors to produce written plans for providing post-trial care, guaranteed by the host countries. This requirement is being applied to treatment and prevention trials. Their definition of care is forthcoming. "Host countries must say that they will be responsible for patients

that leave the study, although what that means, we don't know. Hopefully, there will be some clear guidelines. This has definitely become a barrier [to conducting trials]," said Fanning.

In the past, DAIDS sought support for a consortium-style approach in which industry, host countries, the NIH and others would work together to create a study insurance fund. In this proposed collaboration, the host country would supply personnel and infrastructure; the trial sponsor (pharmaceutical manufacturer) would supply drugs or financial contributions; and the NIH would manage the fund. This proposal was rejected by several of the parties, for reasons Fanning reviewed below.

The pharmaceutical industry, according to Fanning, said "We won't provide post study treatment. We have been held responsible [in the past] for not providing drugs for treatment for life. We want to stop these problems before they begin [in the HIV context]."

Another consideration is cost. In HIV treatment trials, where all participants are already infected, the cost of providing lifetime ART can be quite high. Irving Hoffman observed that, "The price tag to provide triple drug therapy for 2000 people—the secondary, tertiary regimens, the monitoring—is huge. Pharmaceutical companies don't want to get stuck with this responsibility." In prevention trials, where there are many fewer infected individuals, the costs could be expected to be lower.

Host countries expressed willingness to participate in the consortium as designed by DAIDS. When asked to make a formal commitment to post-study care, however, many balked at the responsibility, especially in settings where ART and other more complex forms of HIV care, are not yet available. Countries that are willing to make these commitments may not be able to fulfill them.

Host and Outside Investigators face the same issues of cost and feasibility as research networks do. Other concerns that may arise include whether duration of care changes if a trial is cancelled or stopped and what "for life" means in the context of today's ART formulary, which offers a finite combination of drug combinations.

While DAIDS' first consortium proposal did not take hold, the NIH continues to seek commitments from outside partners so that no single group is committed to providing ART "forever." The NIH is also in the process of setting up a foundation to have a place where "we could lobby to funnel funds," Fanning said, adding that this is "beyond an idea. There is a commitment to do that."

E. Common Themes

- **Need to better document "care" provided in the context of research.**

Several participants noted that research projects frequently provide many different types of care and improvements in the local health infrastructure that are never acknowledged or documented. Col Debbie Birsch noted, "Everyone provides additional care, but it's seldom noted because it's not in the protocol and occurs 'below the radar screen.' It's time that we start documenting the improvements we make. A great divide is created by coming back to communities and saying, 'We are not providing care,' when we are."

- **Need to improve understanding of, and connection with, global funding mechanisms such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and the Presidential AIDS Initiative (PEPFAR).**

Current GFATM policy is *not* to provide funds for research. On a country level, however, GFATM funds are supposed to be allocated through a local needs assessment process. Participants observed that in-country research sites could seek to be part of this discussion. Would it be possible for sites to ask that funds be funneled to their catchment area to improve the community-wide SOC, with a reciprocal expectation that the research site would provide technical assistance for scale-up? Or could Ministries of Health be asked to commit specified sums for the families of individuals in trials?

- **Need to pursue consortium-style approaches; understand what different parties are and are not willing to contribute.**

“While pharmaceutical companies are unwilling to guarantee lifetime supply of drugs, many are willing to donate funds for treatment procurement,” said Mary Fanning. “We still think the consortium is a good model. When we looked at in-country costs to provide ART for the first five years after a trial is finished, it came out to about \$1 million a year.”

- **Treatment for individuals enrolled in trials may be shared among family members; trial developers need to anticipate sharing of medication among those with no alternative means of accessing care.**

F. Open Questions

- **Is provision of ART undue coercion?**

This question remains open to debate, and its answer is almost always dependent on the specific circumstances of a trial site. Reider Lie contended that looking at the big picture, “The answer to that is no.” Individuals enter a prevention trial before they need treatment so the theoretical possibility of receiving treatment some time in the future, is not undue inducement. Lei also drew a distinction between **inducement** and **undue inducement**. Many factors may “induce” a participant to take part in a trial, ranging from the desire to help others to an interest in receiving the benefits that a trial will provide. It is only when an aspect of the research encourages someone to accept a risk/benefit ratio that is clearly not in his or her best interest that something becomes an “undue” inducement.

Other participants disagreed, pointing out that communities in resource poor settings have said that even the theoretical possibility of ART provision is undue inducement and could indeed motivate people to take risks that they would otherwise see as unacceptable.

- **If a community perceives an element of SOC to be an undue inducement, is their assessment always correct?**
- **Why focus on ART as the key component of SOC decisions?**

Participants agreed that given the myriad needs of communities in which prevention trials take place, provision of state-of-the-art ART may seem like a misguided focus for SOC debates and discussions. Saul Walker said that access to ARTs tended to be the focus for the vaccine field both because of the research question that vaccine trials are asking and because of political expectations in the countries likely to host vaccine trials. Walker cited the example of South Africa, where the national Medicines Control Council (MCC) requested

clarification of ART access for breakthrough infections during its consideration of proposed vaccine trial protocols. Other participants identified additional factors contributing to the focus on ARVs, including: advocacy around global treatment access; nascent or well-developed treatment access movements in many countries where prevention research takes place; and the involvement of civil society in GFATM country coordinating mechanisms (CCMs).

Despite this, it is important not to focus on ARVs to the exclusion of other critical dimensions of standard of care. Lori Heise pointed out that relatively little attention has been paid to aspects of care that could have an equally important and perhaps more immediate impact on health and well-being. In some communities where prevention trials are planned, even basic services such as adequate treatment for STIs or TB, or prophylaxis for TB and/or other bacterial infections common among HIV positive individuals, are unavailable. Additionally, almost no attention has been given to the care of women who become pregnant during a trial. “In our enthusiasm to bring ARVs to resource poor settings, we must not overlook opportunities and obligations to address other aspects of care,” Heise said.

- **HIV prevention research will identify individuals who have recently seroconverted; should trials treat acute HIV infection?**

There is active debate in the scientific community about whether treatment during seroconversion might help to preserve the immune system (early in infection there are very high levels of HIV in the blood). Participants acknowledged the need to gather more data on whether treatment in this period should be part of the guidelines for trials.

In protocols in which HIV testing takes place every 6 months, the likelihood of identifying acute infection is relatively low. (Among the 103 seroconverters in the HIVNET studies, the average time from seroconversion at study visit diagnosis was four months).² Still, participants voiced the need to learn more about the impact of hitting early with potent regimens when acute infection is identified. Other potential approaches include cheaper immunomodulatory approaches like cyclosporin, which might be more readily available in the developing world.

- **Are there differences between the SOC obligations of microbicides trials and vaccine trials?**

Participants discussed several ways in which microbicides and vaccine trials differ, including the longer length of follow up and the secondary endpoints in vaccine trials. Microbicide trials, on the other hand, may test women for HIV more regularly than vaccine trials, although this varies from protocol to protocol. Microbicides also require screening and care for gynecological conditions, such as cervical dysplasia or cancer — conditions which may be detected during pelvic exams and for which no care may be available in the community. As Heise explained, “The standard has been to provide care only for what you look for or diagnose”. This has meant that studies in which Pap smears are not done have effectively sidestepped the issue of detecting cervical dysplasia and other anomalies. “What are the ethics in that?” Heise asked.

Participants also raised issues around gender dynamics and the ways that vaccine and microbicide trials anticipate and address the consequences of men’s and women’s trial participation, diagnosis with HIV, and use of treatments that may not be available to other family members. One participant suggested that microbicide researchers have, historically, had to confront these issues much more directly than vaccine researchers. In both fields, investigators are now having to make decisions regarding involving participants’ partners in order to facilitate

the VCT process, to get feedback on product use, or to track whether the vaccine has an impact on HIV transmission in volunteers with breakthrough infections.

As these differences were enumerated, participants also acknowledged the difficulty of developing strategies for addressing these fine points in communities in which trials of several interventions are being staged, sometimes simultaneously. Connie Cellum summarized the challenge, noting that, “On a scientific basis I think these trials are different. On a very simple basis, vaccine trials need to look at prevention of disease endpoints. None of the other interventions will influence the progression of disease, durability of immune pressure, or selection of viruses. But it is very hard to make that argument in the field. Scientifically, there is a difference between vaccine and microbicide trials. Ethically, it is not so clear. Pragmatically, there is not much difference at all. If you don’t standardize the provision of treatment across trials, you can forget people wanting to continue in research in the community.”

- **Which treatment guidelines should guide use of ARV?**

If ARVs are provided for breakthrough infections, then trial planners must consider when ARV treatment will be initiated. This is particularly important for vaccine trials, which will look at whether a particular HIV vaccine candidate slows disease progression by tracking viral load, CD4 cell count and clinical symptoms. In a situation where treatment is provided, planners might use “time to treatment initiation” as a secondary endpoint. Different guidelines (US, International AIDS Society, WHO) give different thresholds for initiating treatment. The question arises: Which guidelines should be used?

Looking further, participants pointed out that almost all guidelines give initiation thresholds based on longitudinal data from US or European cohorts. There is little information on the change in time of viral load and CD4 cell counts in many populations where research is likely to take place. As part of treatment provisions, research groups can gather data from the point of seroconversion to treatment initiation so that longitudinal patterns can be studied.

- **Should trials seek to provide benefit to the community, the individual or both? Who decides?**
- **How should prevention researchers define the community consulted about SOC decisions?**

So far, the ethical debate has tended to prioritize the care and treatment of the specific individuals enrolled in a trial, focusing energy on exactly what care should be offered to trial participants. It has also prioritized the condition under study (e.g. HIV), giving far less (if any) attention to the care available to those screened out of the study or to ailments or conditions not related to the study endpoints.

Heise pointed out that community opinions on what constitutes a preferred ethical benefit may vary. Some communities involved in microbicide trials have voiced interest in securing benefits for the collective community, as well as the individual, and have also expressed interest in selecting interventions which are sustainable in the long-term—even if the quality of care is slightly diminished—rather than “best-quality” interventions which disappear at the close of the trial.

To help surface the different value systems that operate in discussions around trial ethics, the Global Campaign for Microbicides is developing a simulation exercise that forces participants to make trade offs among different trial elements in a way that maximizes their notion of justice and fairness. Such a game

could be used with groups of community members, investigators, and others to help them recognize and articulate the the varying degrees of emphasis that each sector may place on things like individual versus group benefits, international equity versus local sustainability etc.

- **Does the prevention field need to have an answer to the ART question in order to move on?**

In general, participants agreed that research into vaccines and microbicides must proceed, even as the fields continue to grapple with the wider issues posed by research ethics and resource inequities between North and South.

H. Conclusion

A strong consensus emerged at the meeting regarding the need to move away from discussions of “ethical” versus “unethical” standards of care for prevention trials. This was fueled by a recognition that strict ethical measures do not, necessarily, require that ART must be provided to individuals who are HIV-negative when they enroll in trials.

The more pragmatic concerns underlying this consensus included the facts that (1) some areas of prevention research, including behavioral interventions, would have to completely redesign study teams to provide ART during protocols and (2) other areas might find themselves unable to meet the financial requirements of ART provision, and so become stalled in efforts to conduct research.

Participants agreed on the need to begin making a distinction between SOC guidelines and nonnegotiable SOC principles. Such a distinction should highlight the differences between policy choices and ethical obligations.

One suggested avenue toward doing this might be documenting the decision-making process used to develop a SOC, including identification of the stakeholders whose input was sought, and any points of strong agreement or disagreement articulated during the process.

Several “next steps” were proposed to follow up on this meeting, including asking that researchers from microbicides and other prevention fields be included in UNAIDS’ 2003 revision of its Ethical Guidelines for Vaccine Trials; and engaging other groups, like the African AIDS Vaccine Programme Community Task Force, CABs and advocacy organizations in a broader discussion of how to develop and implement SOCs.

Footnotes

¹ Aspartate aminotransferase — increased serum levels of which may indicate hepatic, red blood cell or other disorders.

² By contrast, some microbicide protocols include quarterly testing for HIV.

Consultation on HIV Treatment in the Context of Prevention Trials

Program for Appropriate Technology in Health

International AIDS Vaccine Initiative

Friday, February 28th, 2003

Quarraisha Abdool-Karim
Southern African Fogarty AIDS
Training Programme
Department of Community Health
Nelson R Mandela School of
Medicine
University of Natal
Private Bag X7
723 Umbilo Road Durban
Congella 4013 Durban, South Africa
Tel: 27-31-2604277 or 27-31-
2017486
Fax: 27-31-2604307
Email: abdoolq2@nu.ac.za

Emily Bass
(Meeting Rapporteur)
IAVI
110 William Street, 27th Floor
New York, NY 10038
Tel: 212 847-1051
Fax: 212 847-1112
Email: ebass@iavi.org

Col. Deborah L. Birx
Director, Division of Retrovirology
Walter Reed Army Institute of
Research
13 Taft Court, Ste 200
Rockville, MD 20850
Tel: 301 762-0089
Fax: 301 762-4177
Email: dbirx@hiv.hjf.org

Dr. Connie Celum
Associate Professor of Medicine
University of Washington
Seattle HPTU
Harborview Medical Center, Box 359927
Seattle, WA 98104
Tel: 206 521-5814
Fax: 206 521-5828
Email: ccelum@u.washington.edu

Chris Collins
Director
AIDS Vaccine Advocacy Coalition
101 West 23rd Street #2227
New York, NY 10011-2490
Tel: (212) 367-1084
Fax: (530) 380-3822
Email: chris@avac.org

Mary Fanning
Assistant Director for Clinical Research
Division of AIDS, NIH
Vaccine and Prevention Research Program
Bethesda, MD 20892
Tel: 301 402 0847
E-mail: mf271x@nih.gov

Pat Fast
Medical Director
IAVI
110 William Street, 27th Floor
New York, NY 10038
Tel: 212 847-1068
Fax: 212 847-1112
Email: pfast@iavi.org

Lut Van Damme
CONRAD Program
1611 North Kent Street, Suite 806
Arlington, VA 22209
Tel: 703 524-3750
Fax: 703 524-4770
Email: lvandamme@conrad.org

Megan Gottemoeller
Global Campaign for Microbicides
PATH
1800 K St. NW, Ste 800
Washington, D.C. 20006
Tel: 202 822-0033
Fax: 202 457-1466
Email: mgottemoeller@path-dc.org

Barney Graham
Director of Clinical Studies
Dale and Betty Bumpers Vaccine Research Center (VRC)
Clinical Trials Core Laboratory and Viral Pathogenesis
Laboratory
National Institutes of Health
40 Convent Drive
Bethesda, Maryland 20892
Tel: 301-594-8468
Email: bgraham@mail.nih.gov

Lori Heise
Global Campaign for Microbicides
PATH
1800 K St. NW, Ste 800
Washington, D.C. 20006
Tel: 202 822-0033
Fax: 202 457-1466
Email: lheise@path-dc.org

Irving Hoffman
University of North Carolina
School of Medicine
547 Burnett Womack CB # 7030
Chapel Hill, NC 27599-7030
Tel: 919 966-6324
Fax: 919 966-8536
Email: hoffmani@med.unc.edu

Gerald Jennings
Biomedical Research Advisor
USAID
1300 Pennsylvania Ave
Washington DC 20523-3601
Tel: 202-712-1084
Email: gjennings@usaid.gov

Nzeera Ketter
IAVI
110 William Street
New York, NY 10038-3901
Tel: 650 854-9806
Fax: 650 854-1076
Email: nketter@iavi.org

Randi Leavitt
Infectious Diseases - Clinical Trials
Merck, P26-207
770 Sumneytown Pike
West Point, PA 19486-0004
Tel: 484 344-2672
Fax: 484 344-4027
Email: Randi_Leavitt@merck.com

Reidar Lei
Department of Clinical Bioethics
National Institutes of Health
10 Center Drive Building 10
Room 1C118
Bethesda, MD 20892-1156
Tel: 301 496-2429
Fax: 301 496-0760
Email: RLie@mail.cc.nih.gov

Kathleen MacQueen
Family Health International
P.O. Box 13950
Research Triangle Park, NC 27709
Tel: 919 544-7040 x587
Fax: 919 544-7261
Email: kmacqueen@fhi.org

Craig McClure
Consultant, Policy and Vaccine Preparedness
IAVI
110 William Street, 27th Floor
New York, NY 10038
Email: craig@healthhounds.com

Sheena McCormack
MRC Clinical Trial Unit
222 Euston Road
London, NW1 2DA
United Kingdom
Email: sheena.mccormack@ctu.mrc.ac.uk

John Mutsambi
Community Liaison Officer
UZ-UCSF 15 Phillips Avenue Belgravia
Harare, Zimbabwe
Tel: 263-4-704890, 704920, 722620
Fax: 263-4-704897
Email: John@uz-ucsf.co.zw

Mauro Schechter
Professor of Infectious Diseases
Hospital Universitario Clementino Fraga Filho,
Universidade Federal do Rio de Janeiro
Avenida Brig. Trompowski s/n
Ilha do Fundao
Rio de Janeiro RJ 21.941-590
Brazil
Tel: +55-21-2270-3114
Fax: +55-21-2590-1615
Email: maurosch@hucff.ufrj.br

Steve Wakefield
Associate Director for Community Relations and
Education
HIV Vaccine Trials Network
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North,
Mail Stop J3-100
P.O. Box 19024
Seattle, WA 98109-1024
Tel: 206-667-6705
Fax: 206-667-6366
Email: wakefield@hvtn.org

Saul Walker
European Policy Advisor
IAVI
c/o National AIDS Trust
New City Cloisters
196 Old Street
London EC1V 9FR
United Kingdom
Tel: +44 (0) 20 7216-0078
Fax: +44 (0) 20 7216-0111
Email: swalker@iavi.org

Paul J. Weidle
Clinical Epidemiology Section
Division of HIV/AIDS Prevention
National Center for HIV, STD, & TB Prevention
Centers for Disease Control and Prevention
MS E-45
1600 Clifton Rd
Atlanta, GA 30338
Tel: (404)-639-6155
Fax: (404)-639-6127
E-mail: pweidle@cdc.gov

