

**Think Tank:  
Policy and Practice Implications  
of HIV Pre-Exposure Prophylaxis (PrEP)  
in the United States**

**MEETING PROCEEDINGS**

**UCLA Program in Global Health**

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# Table of Contents

Participant List.....	3
Breakout Groups.....	5
<b>MEETING PROCEEDINGS</b>	
<b><u>Day One Presentations &amp; Discussion</u></b> .....	6
Robert M. Grant, MD, MPH <i>The Peru PrEP Study: Safety, Efficacy, Behavior, and Biology</i> .....	7
Lynn Paxton, MD, MPH <i>CDC HIV Chemoprophylaxis Trials</i> .....	13
Susan Buchbinder, MD <i>A Tale of Two Studies: The U.S. MSM Tenofovir Safety Trial and the San Francisco PrEP Survey</i> .....	21
Ward Cates, MD <i>FHI's TDF Trials and Tribulations</i> .....	26
<b><u>Day Two Presentations &amp; Discussion</u></b> .....	31
Breakout Reportback: Optimistic Group <i>(Studies All Point in Efficacious Direction)</i> .....	31
Breakout Reportback: Pessimistic Group <i>(Studies All Point in Non-Efficacious Direction)</i> .....	36
Breakout Reportback: Intermediate Group <i>(Studies Point in Conflicting Directions)</i> .....	40
Michelle Roland, MD <i>American Academy of HIV Medicine PrEP Survey</i> .....	42
Martin Shapiro, MD, PhD <i>Disparities in Care: Implications for Rollout of Pre-Exposure Prophylaxis</i> .....	43
Bibliography of Briefing Materials.....	49
Acknowledgements.....	50

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<b>Optimistic Group</b> <i>(Studies All Point in Efficacious Direction)</i>	<b>Pessimistic Group</b> <i>(Studies All Point in Non- Efficacious Direction)</i>	<b>Intermediate Group</b> <i>(Studies Point in Conflicting Directions)</i>
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## MEETING PROCEEDINGS

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#### **DAY ONE PRESENTATIONS & DISCUSSION: THURSDAY MAY 11**

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**THOMAS COATES:** Our purpose today is to project into the future and think about what might we do should we find out that any of these PrEP strategies may be useful. We think it's a good time to begin thinking about that because, with the results from the male circumcision studies forthcoming (which may have less relevance for the U.S. setting but nonetheless are really groundbreaking) and so many other biomedical prevention trials underway, it could represent a sea change in the way we think about HIV prevention. And we see this as a beginning of thinking about what that might mean in terms of policy, in terms of practice, in terms of what we have been charged with for delivering prevention strategies, and that's really the purpose of this meeting.

I want to thank the funders of this meeting -- The John M. Lloyd Foundation (we're happy today to have Trish Carlin, who is from the Elizabeth Glaser Pediatric AIDS Foundation, but on the board of The John M. Lloyd Foundation; and Heidi Lloyd and Melanie Havelin from the board of the John M. Lloyd Foundation, we thank them for their support). Also, the Diana Princess of Wales Memorial Fund, The Franklin Mint Foundation, the UCLA AIDS Institute, and the Center for HIV Identification, Prevention, and Treatment. So we appreciate everyone's support for this meeting.

I'm thrilled that you're all here. It's really an interesting gathering of people representing a diverse set of backgrounds, and that was the deliberate mix that we wanted to have. So let me say a little bit about the agenda for the day. We'll start with the two presentations from Bob Grant and Lynn Paxton on the current trials, and this will bring us up to date as to where these trials stand, what their current thinking is, what their current progress has been, and I've asked the speakers to also think about the implications of those trials or some of the lessons learned from those trials. We've deliberately left sufficient time for discussion -- we want there to be ample time for questions and discussion in a large group. After the break we'll have a presentation by Susan Buchbinder from San Francisco and Ward Cates from FHI on the trials in San Francisco/Atlanta and in Africa. Then this afternoon we will go into our breakout sessions, and we've deliberately selected the areas we want to cover. We want to think about three scenarios. What if the trials come out with a highly efficacious finding, a moderately efficacious finding, or a low-to-no efficacious finding? What are the implications of the current trials for future research and for prevention programming? For funding and for capacity building? What do clinician and prevention providers need to prepare themselves for? What are the issues for media relations and communications? And if anybody can think of any other bullets that we should add to this list, we can entertain them before we go into the breakout sessions.

For the breakout groups, we have engaged the services of our breakout group leaders, and we have prepared them for their task. We wanted them to be able to give some thought to this prior to

coming to this meeting. Group 1 (low PrEP efficacy) will be lead by George Ayala from APLA and the Institute for Gay Men's Health, and Trish Karlin from the Glaser Foundation. Group 2 (moderate PrEP efficacy) will be lead by Shari Dworkin from Columbia and Jeremy Sugarman from Hopkins. Group 3 (high PrEP efficacy) will be lead by Bart Aoki from the Universitywide AIDS Research Program, and Agnès Fiamma, who runs the UCLA research office in Johannesburg.

Then tomorrow we want to begin to talk about another set of issues related to the implementation of prevention and particularly the implementation of biomedical prevention, and that has to do with disparities. We all know in this country that there are disparities, that people who are African American or Latino are more likely to get HIV. If they get HIV, they are more likely to get inferior treatment, and so we've asked Martin Shapiro, the leader of the HCSUS study from our faculty at UCLA, to talk about some of their findings and to think about the implications of those findings for how we might implement PrEP in an equitable way, particularly reaching those groups of people who most need preventive interventions.

Finally we will focus on recommendations that various policy-funding agencies should enact now, and that will conclude our day tomorrow. We will be issuing a report from the meeting and possibly also a journal article. I also want to remind everyone that there are journalists present. Jon Cohen is here, whom you all know and respect, and Daniel Costello from the Los Angeles Times may be here as well. They are here as reporters, so if there is anything that you don't want to be quoted as saying or any data that you don't want to have publicized, bear that in mind.

Without further adieu, let's move on to our first presentations with Bob and Lynn.

### **PRESENTATION BY ROBERT M. GRANT, MD, MPH**

*The Peru PrEP Study: Safety, Efficacy, Behavior, and Biology*

**BOB GRANT:** Thank you Tom. It really is a pleasure and an honor to speak in front of such an esteemed group of people all interested in something that's quite interesting for us. I'll be focusing on what we used to call the Peru PrEP Study, the study that will evaluate safety, efficacy, behavior, and biology associated with daily oral chemoprophylaxis. The study is supported by the NIH and involves a consortium of organizations, including the Gladstone Institute, UCSF, Impacta (in Lima); the Asociacion Civil Selva Amazonica (in Iquitos), and more recently the Fundación Ecuatoriana Equidad (in Guayaquil, Ecuador). The inclusion of Ecuador is an exciting new development in our study plans. They have a significant epidemic and excellent track record in being able to study it and to mobilize communities for both prevention and research. It does mean that we'll have to change the nickname for the study. We had deliberations, and I think now we should really be referring to it as the Andean PrEP Study.

We're proposing to enroll 1,400 high-risk men who have sex with men, randomized one-to-one to receive chemoprophylaxis (PrEP) versus placebo. Participants will be followed on drug for 72 weeks and monitored for HIV infection, adverse effects (especially renal and liver), risk behavior, and sexually transmitted infections. A subgroup of 200 will be monitored for bone marrow density and fat composition. If a person becomes seropositive, we'll look at drug resistance and immune responses.

What is the PrEP study drug? We're currently planning to use Truvada, a formulation of emtricitabine (FTC) and tenofovir. This is based on data from 2004 and 2005. We came to understand that tenofovir was only partially effective in nonhuman primates after repeated exposure to simian immunodeficiency virus. This was presented in Bangkok in 2004 and more

recently by the group from CDC in 2005. In addition, we're aware that, from our broader experience with antiviral drugs and HIV, that combinations of drugs can increase the efficacy and decrease resistance in very different settings. We're also aware of safety data suggesting that the addition of emtricitabine does not add substantially to safety concerns compared to tenofovir alone. So this information taken together led us to propose the use of the coformulated combination. I think that this decision may be of interest to you -- it does have implications for other studies; we're aware of that. So we did struggle with the question "Should all clinical trials with PrEP use the same agent?" and we considered that maybe we should use tenofovir just because there were studies already in the field based on tenofovir. And I think that the following perceptions really influenced our decision to use the combination. I think we all have to appreciate that these are early days for PrEP and that's really science code word for "we do not know very much about PrEP right now."

For example, we do not know whether monkey models have added value for understanding what's going to happen in humans. It may be that tenofovir alone will be sufficient in people. It may also be that the combination of emtricitabine and tenofovir may have better efficacy. We do think that it's unlikely to have less efficacy. The combination does pose a risk of emtricitabine resistance, which is an additional risk. But we also have to admit that maybe neither will turn out to be effective based on the current clinical trials. And really since we don't know very much about PrEP right now, I would argue in principle that diversity in the research program is helpful essentially because it increases the chance that we may discover something useful. We wanted to design a study that would show us whether the combination of emtricitabine with tenofovir was better than tenofovir alone. So we considered a three-arm efficacy study to try to nail that down. But as is often the case, the statisticians burst our bubble of fantasy by pointing out that such a study probably would require 30,000 participants, which far exceeds both the current and the projected capacity of prevention research in the world. So it appears to be that we will not be able to design a trial that would ever prove whether combined PrEP is better than one drug alone with respect to efficacy. Now, studies with respect to resistance or safety may be feasible, but efficacy is going to be difficult to do in three-arm studies.

I want to focus on some data that we actually have at this point. I recently completed data collection on a formative phase of our research, and I think that this data plus the perspective that we've gained over the last several years in PrEP research has really emphasized the importance of communication, and it's not just messaging for the media. I've come to believe that communications and community building are the basis for successful HIV prevention and prevention research. So I very much agree with the health educators and activists on the streets of Iquitos who ended their presentation by saying, "Let's communicate. This message had nothing to do with research. They were saying, "Let's communicate as a way to prevent HIV."

The study involved four community advisory boards. One CAB actually met eight times over the course of last year. What have we learned? Well, what we've started to learn is that community consultation is not always straightforward. In fact, communities are segmented in many important ways. Civil society contains opinion leaders who have no specific interest in HIV, and others that are primarily interested in HIV. The at-risk populations in our proposed study sites are also segments. They're all men who have had sex with men, but they also include a variety of different segments including *Buses* (straight-appearing gay men), *Deschavados* (gay-appearing gay men), *Travestes* (transvestites/transgenders), and *Mostaceros* -- which are hard to translate; you might call them hustlers.

The professional community is also segmented. We've got medical professionals on-site. We've got research sponsors and research investigators. And I assure you there isn't the common mind among this particular group either. And then political leaders who attempt to try to bring together

all these people. So what did we learn from them? One important issue is that people are thinking very differently about ethics. And there are at least two ethical principles that are in play – beneficence and autonomy. When sponsors talk about ethics, they talk about it as inducement, but when we talk about ethics, we talk about benefits. And it seems clear from our work in Peru that target populations focus mainly on the benefits of research, including asking for higher visit reimbursements -- at least to a level sufficient to compensate them for travel and time lost from gainful employment. They also want more medical care to be part of their resource programs.

Many opinion leaders in contrast focus most on autonomy; so if anything, they want lower visit reimbursements, but interestingly they also want the study to take care of the study participants' medical care.

So there's clear common ground here in that all groups appear to want to see some evidence that the study investigators and sponsors are prepared to provide some basic medical care to study participants.

In fact, I think that there are really four principles that need to be at the basis of clinical research: autonomy, beneficence, social justice, and fidelity. And how we weight these is very different in different communities. For example, I think good clinical practice as code by the U.S. primarily protects autonomy; and that beneficence, social justice, and fidelity are left for other consideration. However, our study subjects, as I indicated, are primarily interested in beneficence, social justice, and, interestingly, fidelity -- which is really the primary focus of ethical research considerations in anthropology. That is, fidelity to the target population is also something that is of a great interest to everyone that we talked to. So it's important that we understand that when we talk about ethics, in many cases we're talking in ways that differ greatly from how our study populations perceive the issue. There were also differences in informed consent. Some opinion leaders were skeptical about whether genuine informed consent was ever feasible. In contrast, HIV activists and CAB members invested long hours to revise the consent forms word-by-word to ensure comprehension. Potential study subjects, on the other end of the spectrum, wanted more information. Not dumbed-down information, they wanted more information, and they trusted their own ability to understand to defend their own interests.

It became clear that successful research was going to require building bridges of communication between segments of the community at our study sites. There was concern that PrEP could cause disinhibition that might increase risk behavior. Participants in HIV vaccine research also expressed concern about disinhibition, which I think reflects the success of the vaccine research program in emphasizing the importance of this issue. It's important that the majority of people we talked to did not express any concern about disinhibition. Specifically, HIV service providers and HIV activists including visibly gay men, transvestites, and hustlers either did not mention disinhibition as a concern about PrEP, or specifically said it was not an issue of concern. It is a concern to us. We will assess risk behavior in our study in several ways. We will evaluate STDs (gonorrhea, *Chlamydia*, syphilis, and herpes) every six months. Behavior will be assessed by computer-assisted structured interviews accessed before, during, and after the PrEP use, including two visits (two months and six months after finishing the PrEP dosing). The questionnaire will be designed to try to assess if a pill a day increases risk behavior, or rather does it decrease risk behavior. We think that a pill a day might actually decrease risk behavior if it serves as a daily "I am at risk for HIV" reminder. It could also foster a disclosure of HIV status in the population, which could turn into lower risk behavior rather than an increase. In addition, we think PrEP may have an effect on sexual network characteristics.

There is reason for optimism. This is data from Michelle Roland's PEP study. I see she's in the audience. She'll tell you later if I've misinterpreted this. We've seen in general that risk behavior

declines with PEP, providing that it's also given with counseling. This is the data that Michelle studied, published by Jeff Martin in *AIDS* in 2004. And you can see that after open-label PEP is offered, reported high-risk acts actually decreased in the population. So there wasn't any disinhibition in the outset. There was decreased risk behavior. So was this emblematic of counseling effectiveness or in fact does 28 days of combined antiretroviral therapy make using condoms look and feel good.

Overall the insights from our communications activities are that communications in theory can help identify distinct groups by what they say. Scientist versus community is clearly a too-simple formulation of a problem, but I also think that simply saying that there are many communities is way too vague. I think we can actually be very specific about which communities are out there and what we need to know about what they're saying. I also take full responsibility for this. Consultation should build communities, and I am a strong believer that meetings should be held primarily at study sites, where the richness of the community can be fully represented. I am concerned that international consultations may be misleading and potentially even disruptive

Another point is that recruitment begins long before the study starts. Community development is clearly an important part of the activities of our partner in Peru – Impacta Salud y Educacion -- which does workshops, open houses, community education, and sports. Their premise is that a mobilized community of men who have sex with men would in fact demand research that bears directly on their health needs.

Another unique feature of the Peru trial is that people with hepatitis B will be included in the trial. Both of the agents that we're using are active against hepatitis B. There could be some therapeutic benefit, including a decrease in hepatitis flares while on the drug, but there also could be a risk of flare when stopping the study drug. We think that the risk may be much lower when starting with normal or near normal LFTs like those in our study. The risk of hepatitis B drug resistance will be minimized by the use of two drugs. Tenofovir itself poses a very high barrier to HBV resistance, and very few cases have been reported. Participants will know their hepatitis B status prior to enrolling in the study because of the special risks and benefits associated with participation.

So why did we choose Peru? Peru is the origin of peppers, pisco, potatoes, tomatoes, and ceviche. Outstanding food. But also Peru is in Latin America, which is the third most HIV-impacted region. This is the map from *Science*, highlighting the continents that are most impacted by HIV -- Africa, then Asia. This is in contrast to the places where most HIV research is done -- Europe, North America, and Australia. I think that the PrEP program has tried to remedy this problem by doing research in diverse locations.

We also have in Peru outstanding collaborators. These crews have been able to identify very high-risk men with incidence rates that run approximately 5 percent per year. Now, this isn't to say that the HIV incidence is higher in Peru than it is in other places. This is just to say that the investigators there found ways to identify the highest risk parts of the MSM community. It is a subtype B epidemic, which makes our immunological studies easier. It also could be make it more relevant to the U.S., despite being one country that has enormous genetic diversity in the human population based on immigration. The projected HIV incidence in Iquitos and Lima was estimated as follows: We had cross-sectional surveys in the 1990s showing HIV incidence of 6 to 12 percent. At that time these were relatively "unintervened" populations. In later years the cross-sectional survey showed the evidence that the incidence may have dropped to 4 to 6 percent, and this may reflect benefits of mass media messaging.

More recently our collaborators have established prevention trials that have demonstrated HIV incidence between 3 and 5 percent (average 4 percent). And these are groups now who use

condoms and counseling. So the assumed incidence for planning the Peru PrEP trials is 3 to 4 percent. How much power does that give us? Well, assuming 4 percent incidence we have almost 90 percent power to detect 60 percent efficacy. If incidence is really 3 percent in the study population, we still have 80 percent power to detect 60 percent efficacy. So we're looking for high levels of efficacy in this first-generation study. This is based on insights from our very preliminary analysis of cost-effectiveness where we ask the question "Can future PrEP roll-out be economically feasible in all countries?" We wanted some assurance that at least there's a fair chance that it would be economically feasible in countries where we do these studies. Clearly, this is very speculative. It's a "what if" kind of analysis. It depends in huge part on what is found during the clinical trials. The price of tenofovir is decreasing around the world. This is data from Gilead, compiled by Kate McQueen from Family Health International. Based on this, plus assuming adverse event rates in uninfected populations are equal to those in treated populations and minimal requirements for laboratory monitoring, we estimated (I would say in an optimistic scenario) that PrEP would cost \$256 per person a year. You can see that the cost-effectiveness for a large portion of this parameter is reasonable and favorable. It fares well compared to needle exchange, for example, which is thought to have cost effectiveness of about \$20,000. It probably is a little worse than voluntary testing and counseling, but it's much better than occupational postexposure chemoprophylaxis, which is expensive but clearly a reasonable and an accepted level of expense to prevent HIV acquisition in health care groups. So Peru populations we think have about 5 percent incidence, not in trials but the population generally, and that would give us an estimated cost that would be less than \$10,000 per HIV case averted. We think this is a favorable cost-effectiveness.

In addition, our program includes a careful analysis of drug resistance and viral load. PrEP resistance would be measured by genotyping as well as phenotyping. Management of seroconverters has been a hot topic in this field. In our study the study pays for primary care for HIV/AIDS by HIV/AIDS specialists (which the group in Lima thought was extremely valuable). The study pays for CD4 and viral load testing, genotyping, as well as cellular and humoral immunology. The Global Fund, which is giving grants to both Ecuador and Peru, will pay for ART if it's needed by seroconverters. In addition, the study is supporting community-based ART initiatives through teaching/lectures, building laboratory capacity as well as CD4 cell counting in areas where this is a significant barrier for the initiation of life saving therapies.

It seems clear to us, because people are focused on benefits and social justice that our study and our activities need to contribute to getting people on treatment in these communities even if they are not in our study. One way we plan to do that is providing laboratory support, which benefits those at-risk groups. We are not saving money in a bank account for future ART use. Other study programs have done that, but we personally believe that that is inappropriate given that there are people now who need treatment.

We're also interested in whether chemoprophylaxis will have immunologic benefits. Two animal studies raise the hypothesis that viral antigen exposure during tenofovir chemoprophylaxis may induce antiviral immune responses that could provide future protection, or attenuate the course of infection among seroconverters.

This is a collaboration funded by DAIDS but between CDC-sponsored sites in the U.S., FHI-sponsored sites in West Africa, and NHI-sponsored sites in Peru. The timeline for the Andean PrEP Project really started in February 2004, with our first meeting with the Community Advisory Board. After that, there was 26 months of communications between investigators, sponsors, and the communities. Just this month the United States approved our protocol. I'm very about that. And we expect the enrollment to begin fourth quarter of 2006, to be completed in 2007. The study is to end in 2009.

I'd like to thank the huge number of people involved in this study. I won't do it by name, but really it's an excellent team. It's a joy to work with them. They're all very good at what they do. And I'd like to end with part of a poem from a Peruvian poet in Spanish for you to read. I will read the English translation. The poem is called "The Nine Monsters", and it was written by César Vallejo in 1939. He finishes by saying, "Mr. Minister of Health, what to do?... There is, brothers, so much to do."

Thank you.

**THOMAS COATES:** Thanks Bob for a beautiful presentation. I did want to mention that we had invited your Peruvian colleagues to attend this meeting -- Javier Lama, Pedro Goicochea, and Jorge Sanchez. Unfortunately, weather conditions in Lima are worse than weather conditions here, and the low fog has kept the planes from coming. Maybe what we can do is take a few minutes, not for discussion so much but any clarification questions that people might have for Bob, and then after Lynn Paxton's presentation, we'll engage in a more complete discussion.

**BOB REMIEN:** I'm curious about the testing for participants, I assume it's antibody testing? I was wondering if you were testing for acute HIV infection, and if not, what's the thinking behind that window period before they might seroconvert?

**BOB GRANT:** The patients are tested four times at two different time points prior to initiating PrEP. All with antibody tests. Given the incidence, the chances that any one of them will be in the window period from the time they start is small. In addition, they'll be tested again within one month after starting PrEP. We know from the Phase I/II studies that one month of exposure to tenofovir while on therapy is not sufficient to cause drug resistance in populations of viruses in humans. We considered using our main testing as an outcome for this. The problem is that it's not readily available in a majority of places where the epidemic is or PrEP is being used. There is an important question as to whether PrEP could lengthen the window period. There's no evidence that that is the case, but I think that that is an important possibility that needs to be considered in these trials. Where we've handled that is by measuring the antibodies one and two months after people stopped PrEP, so that if they were in a window period at the time they stopped PrEP, that window period was prolonged because of the PrEP. We should see evidence of seroconversion after they stopped.

**QUESTION:** Bob, the four ethical principles you mentioned -- I noticed that altruism was missing, and I'm just curious about the guidance for both research subjects and investigators.

**BOB GRANT:** Altruism I see as a motivation for participating in research. It's an important motivation, and I think that people can see that the study provides benefits but also defends social justice or promotes social justice, and I think it becomes easier for the altruists. The ethical principles -- the way I formulated them -- were protections that the studies should offer the study subjects. You're now talking about motivations that the study subject can offer research, and I think that those are very important to consider. But I would say altruism is really going to be easier when people can see the social justice in the research.

**AGNES FIAMMA:** I'm wondering did you consider or are you doing anything about partners of those that are participating in the trial?

**BOB GRANT:** Routine STD management at all of our study sites includes STD evaluation and treatment of sexual partners who are voluntarily referred by the participant. In addition, we ask each participant questions about their sexual partners to try to understand their sexual network.

We are not including direct observations of the partners except how many of them have STDs. But I think you're asking a very good question. Could PrEP not only benefit the individual who takes it, but also his/her partners. Theoretically, yes. Do we have some experience with partner study designs? We have not included partner evaluation in the study, which is already quite complex as you can imagine.

**RENEE RIDZON:** One of the questions that's come up with regards to partners in a number of the prevention trials has been -- should you try to circumvent to then actually testing the partner? And then also the screening process -- when people screen out, whether or not the testing should also be offered to the partners?

**BOB GRANT:** I agree with that as a practice standard, actually. As I said, we continually offer evaluation and treatment of partners of people who get gonorrhea, *Chlamydia*, herpes, so why not HIV? It's another STD. So it makes sense in terms of practice standards, and the research information would also be very important. Again, it's not a formal part of our protocol, but it is an appropriate practice, and I agree with that.

**JON COHEN:** Given the incidence in this population, what are you doing to evaluate pre-existing immunity at baseline?

**BOB GRANT:** We're collaborating closely on the DAIDS-funded study with Douglas Nixon. He's an immunologist with the Gladstone Institute. He's primarily evaluating specimens from San Francisco that have been gathered through or in collaboration with the CDC investigators. We're looking primarily for evidence of cell-mediated and natural killer cell responses directed toward HIV antigens in those who were seronegative at the time that they started the study.

**JON COHEN:** Are you doing that in Peru, though?

**BOB GRANT:** We will do that in Peru. We haven't started the study in Peru yet.

### **PRESENTATION BY LYNN PAXTON, MD, MPH**

#### *CDC HIV Chemoprophylaxis Trials*

**LYNN PAXTON:** I'm going to be talking to you today about the status of the CDC PrEP studies, mainly in Thailand and Botswana. I was very aware that I was going to be following Bob and that he was going to be covering a lot of the general issues; also, Susan Buchbinder is going to be talking in depth about our domestic safety study in Atlanta and in San Francisco. I'm going to be covering more general issues about our efficacy studies, and I'm going to talk a bit also about what CDC is planning in terms of the question that we're here to talk about today. The "What if it works?" scenario or "What if it doesn't work?" scenario as well. I'm mainly going to be dwelling on the CDC PrEP studies that are going on internationally and the consultation that we had in December 2004, and plans for further consultations and how we're analyzing all the information that's coming out of consultations such as the one we're at today.

As you well know, we don't have an HIV vaccine. We don't have a microbicide. And there are a lot of indications that PrEP may be biologically feasible and might work. HIV infection does not occur immediately, and so there's a certain theoretical possibility that if we intervene early enough that we could either prevent it totally or modify the virus/host interaction.

I always bring up the point that this is not a new concept. I remember back in 2002/2003 when we were really starting to think about the options of HIV chemoprophylaxis, I would mention it to

people and they would be aghast, and I would ask them "Well, how many of you have put your HIV-infected patients on prophylaxis for opportunistic infections?" We do it all the time. And, you know, if you make that switch in your mind, you might better understand where we're coming from with HIV chemoprophylaxis.

HIV postexposure prophylaxis for occupational exposure has become routinely used. It's based really on one particular study showing 81 percent risk reduction from using AZT alone. And so HHS and CDC has long made it a recommendation to treat under certain circumstances for occupational postexposure chemoprophylaxis, and as of the end of 2005 we have actually put out recommendations for treatment of nonoccupational exposure to HIV.

Tenofovir was approved in 2001. I think Truvada was approved in 2004. At this time -- this is an outdated slide -- they've had more than 12,000 patients on tenofovir clinical trials, and we're well over the 200,000 mark in people in clinical settings. I was actually totaling up the number of my own patients that I have on tenofovir and Truvada, and it's already over 60 percent. In fact, when I have a new patient, we almost always give them a tenofovir-containing regimen because we found that it's well tolerated, that a lot of the patients like the ease of administration; and, as you all know, there's a relatively low level of resistance.

Bob has already talked about some of the primary concerns we have with HIV chemoprophylaxis, and we take this all incredibly seriously. Although we have also found that some of the potential participants are not as worried about these things as we are, but we feel that it's very important that we investigate these. The primary one is behavioral disinhibition, and there is some evidence from studies that were done in the era of extensive HAART availability that there have been some increases in risk behavior. Some research indicates that a relatively small change in risk behavior could negate any prevention benefits that you might have gotten from HAART. And although it's quite clear that in previous trials we've actually seen that there have been decreases in risky behaviors in MSM.

I'm a big believer in looking within the trials at any changes in behavioral disinhibition, but we've got to be realistic here -- these are trials in which people are getting intensive risk-reduction counseling which they otherwise wouldn't necessarily be receiving. Also, these trials contain a placebo, and so people are well aware that they may or may not be getting active drugs. But frankly, I think it's only going to be in postmarketing studies that we will actually know. Because by then you'll also know what the level of efficacy is from the trials. I think it's going to have a very significant impact on how people behave. If you know that something is 40 percent effective, you might behave a little differently than you would if you knew that something was 90 percent effective in the trials. So I urge a note of caution. We look at these things within the trials, but I think we have to accept it for what it is and realize that it's probably in the postmarketing phase that we will get better information about actual use and disposition.

Another thing that's very interesting is that these studies have a strong ongoing safety component, and we believe that tenofovir has been shown to be very well tolerated in HIV-infected persons. We believe that it's likely that, in HIV-infected people who are on fewer medications and are generally healthy, that we will see fewer adverse side effects.

But as you know, tenofovir has been associated with decreased renal function, decreased bone marrow density, and some gastrointestinal side effects, among other things, and we're going to be closely monitoring all of those within these trials. We're going to be monitoring very closely behaviors, toxicities, and resistance in all of these trials.

This is what the current status of tenofovir trials is. Ward is going to talk about the trial status of the FHI trials, but as you can see, there's quite a bit of red on this slide showing trials that were either stopped or never got off the ground. But the ongoing CDC studies are the domestic study in Atlanta and San Francisco; our Botswana study is currently on hiatus because we have made a decision to switch from tenofovir to Truvada within that trial; and our Thailand study is of tenofovir.

So to get to the meat of my presentation, I'll talk about what's going on in Thailand and Botswana. Now, I should start off by saying that CDC is part of the U.S. Government, and in our field stations we actually work government to government. So these are collaborations with the government. In Thailand our collaboration is directly with the Thai Government; more specifically we work with the Bangkok Metropolitan Authority.

The Botswana field station has been in existence for about ten years. It started off primarily as a TB field station, and then HIV has become a greater force there. The study is going to be taking place in the capital (Gaborone), and in the second largest city (Francistown).

There are some commonalities between the two studies. Both of them are Phase II/III randomized, double-blind studies in which participants have a one-to-one chance of receiving study drug or placebo. For each of these studies, after the first 200 person-years, there will be a DSMB review. In fact, the Thai study is to be reviewed sometime later this month. The objective of this review is to take this first look at the data and make sure that there are no significant safety concerns. Presuming that there are not, then it will go into a full Phase III efficacy trial. But I must state, it's an artificial distinction to say it's a Phase II then on to a Phase III, because the safety evaluation is continuous throughout the trial.

In each of the studies, participants undergo screening and enrollment visits and are seen monthly. In addition, at their quarterly visits, they have more intensive interviews and physical examinations. They have an interview at each visit. HIV testing is monthly. They have risk-reduction counseling basically monthly. They also have adherence assessments and side-effect monitoring monthly.

The end points for both the trials are HIV seroconversion, adverse events, risk behaviors, and adherence. For those few numbers of people that we expect to seroconvert. We'll be looking at altered viral set point.

We started enrollment in June 2005 in Thailand, and we are now at around 900 people out of the projected 1,600. We had begun enrollment in October 2005 in Botswana, and then in February we started to talk about whether or not we should change over from tenofovir to Truvada. Bob gave an excellent presentation of some of the things that went into our thinking about this, and we made a decision that, because at that time we had relatively few people involved in the tenofovir trial, that there was still an opportunity for us to switch over and to test Truvada because we think that it's a good thing to test multiple interventions in this field. The decision was discussed extensively with stakeholders inside and outside of the country. The study went on hiatus in March 2006, and we expect it's going to restart in September 2006. During the period that we're on hiatus, participants who were involved in tenofovir studies are continuing on that study. That's still ongoing, but we're not taking any new enrollments. And when we restart we'll be calling it the "Tenofovir-Plus Trial". Participants will be switched over from tenofovir to Truvada.

So there are some design differences between the studies, and these are very important. In Thailand there is a lower HIV incidence. We project it is around 3 percent, and we're aiming for a total at the end of about 1,600. And the study population is HIV-negative injection drug users

(who must have used within the past six months) aged 20 to 60 years old. The demographics of drug use in Thailand trial are about 88 percent men and 12 percent women.

Assuming a 67-percent reduction in HIV, we have about 87 percent power, presuming an incidence of 3 percent. We're allowing about 15 months for the enrollment period, and originally we had planned to follow participants for 12 months, and then people would come off the drug, but we have since put an amendment in -- which has been accepted -- seeking to keep all participants in the study until the last person has completed 12 months. And then we anticipate that we'll have about a six-month closeout period.

In Botswana our population is HIV-negative heterosexuals who have had sex within at least the past three months. And because this is a wide-ranging epidemic that primarily affects younger people, we are concentrating on 18 to 29 year olds. It's 50 percent men and 50 percent women. It's not a couples study, though -- people enroll individually, although there's no prohibition if your partner enrolls in the study. We estimate that, assuming an HIV incidence of 5 percent, there's at least an 80-percent power to detect a 65-percent reduction of HIV. Again, we're anticipating a 15-month enrollment period, following everyone until the last person enrolled has gone 12 months and a six-month closeout period.

In Thailand, most of our recruitment has come through a prior extension study in which we had a lot of people who wanted to join the trial, and then we're doing a peer referral. We're also now branching out into the community and doing much more community recruitment, and that has really paid off. We had a very -- perhaps in some cases a little bit too -- brisk enrollment. It got to the point where we couldn't quite handle the number of people that were coming in every month, so we've had to scale back a little bit. We have a community relations club with IDUs and an external advisory board, although we have still had complaints from certain groups that we haven't engaged everyone that would like to be involved in this, and so we have expanded our efforts. We have engaged a specific community liaison person. We have established a working group. We have made outreach to all the groups that have had complaints about the way that we have engaged people. We're hoping to make headway on that.

We are linked to the Ministries of Health in each of these countries, and one of the key things that has been good for us in comparison to some other trials is that we're working with countries where the Ministries of Health already made the commitment to provide antiretroviral therapy to their HIV-infected citizens, and so in both of these places, people who meet the criteria for treatment will receive it through the local Ministries of Health. In addition, we do provide coverage for any adverse events that occur within the trial. In Thailand the Bangkok Metropolitan Authority covers any adverse event and CDC reimburses them for that. In Botswana the Ministry of Health just took on the whole thing and said, "We'll just cover your needs for adverse events."

In Botswana our main recruitment is coming through the voluntary counseling and testing centers that CDC also helps set up and continues to support to a certain extent. We're also getting people out of the STD and family planning clinics, and a lot of work is going into local recruitment. We've got radio, print, and TV ads. The best ways of getting people to find out about the study has been to go to the local shopping malls, which are a big thing. We have a series of community and participant advisory boards that have been set up. And Botswana is -- if you want to make a generalization about culture -- is a culture that puts a great emphasis on consensus and meetings and talking things out; so we've had a series of community meetings to explain the study. We well recognize that you can't engage just potential participants. You really have to engage the entire community, and we've done a great deal with that.

I'm going to finish up by talking a bit about the consultations we've had CDC's plans for eventual development of guidelines and implementation. We've talked a lot in the past about vaccines and microbicides and how to implement them, but there's a key difference here that we need to keep in mind because tenofovir and Truvada are on the shelves right now. In contrast, if you had a vaccine that was proven to be effective, there's still going to be a certain amount of time that you're going to need for manufacturing and scale-up; it would not be something that people could just go down to their local provider and get. That is not the case for tenofovir and Truvada. It has been said that the minute that any of these interventions is proven to have any level of efficacy in any of the trials, that people are going to get it. The minute we make the announcement, in certain areas they're going to be going down to their local provider and trying to get it.

At the end of 2003 and beginning of 2004, we started to think about what we need to know and do to prepare ourselves, and in December of 2004 we had our first CDC/NIH-led tenofovir consultation in Atlanta. You have the summary document in your packets, but basically we want to look at the impact of demonstrated efficacy in one trial on other trials, and to start thinking about what HHS recommendations for tenofovir use in the U.S. would be. To make those recommendations, we would need to consider the efficacy level, the different transmission routes, and any unstudied populations. We would also need to think about how we would start monitoring for increased risk behavior, HIV incidence, adverse events, and what the impact on any existing domestic and international HIV prevention programs, as well as future vaccine and microbicide trials, and to start thinking about future HIV PrEP research with other ARVs, other dosing schedules, and other delivery systems.

Since this consultation occurred in 2004, I've been very gratified to see that there have been a number of groups that have started to step up to the plate on these issues, today being one of them. A sponsors group has been meeting on a regular basis to start discussing some of these issues. The Forum for Collaborative HIV Research is now starting to put together a steering committee to bring together people from the various prevention groups -- vaccines, HSV, male circumcision, PrEP -- to look at these things as a whole in terms of ongoing research recommendations and potential prevention packages that could be put together. The Global Campaign for Microbicides is going to be sponsoring a meeting to talk about the ethics of PrEP and whether or not it should indeed become the standard of care if it is shown to be effective in the current trials. And it seems like almost every other week now I'm getting approached by someone who is starting to think about this, and I'm very gratified by this because it shows people are starting to think about this and make plans. It will be our role at CDC to think about and to start writing guidelines, at least for the U.S. population. As we know from all the other guidelines that CDC and HHS has put out, these guidelines are often also used in other countries, and so we are very cognizant that these guidelines will probably not just be for the U.S., but that other people will be looking at them as well.

CDC is also one of the major implementers. Through our system of field stations and other venues, we will be also one of the major implementers for any these programs. And so our plan is that we will attend all of these meetings and will gathering the information that comes from them. We'll be looking for any gaps from these various meetings that we might fill in terms of having other consultations to look at this and using all this information to help us with guideline development and implementation recommendations. So that is some of what we are planning at the moment.

My conclusion -- and this slide really hasn't changed since I've given this talk ages ago -- is that we firmly believe that this assessment of tenofovir and Truvada as HIV chemoprophylaxis is really the rational next step at this point in time for HIV prevention research. We feel that at CDC like we're really conducting some groundbreaking and complementary research. We have the

monkey studies that Bob has referred to that we're continuing to expand upon and to use to help elucidate some questions out there, and we have complementary studies at looking at MSM populations, IDU populations, and heterosexual transmission. And for the moment we think that it represents one of our best hopes for an effective biomedical HIV prevention tool in the near future, as we wait for other tools such as microbicides and vaccines to come upon the scene as well.

**THOMAS COATES:** Thank you, Lynn. One of the things I was concerned about in Bob's presentation was that we would have different drugs used for different routes of transmission, and the fact that the drugs are being harmonized so that Truvada would be used to look at prevention by all three routes of transmission I think will be very important.

**LYNN PAXTON:** We are actually not using Truvada in the Thai trial. It is tenofovir.

**THOMAS COATES:** And it's going to be tenofovir all along?

**LYNN PAXTON:** We were already over half enrolled by the time that we started thinking about whether or not to switch over to Truvada. For various reasons it was good to continue to look at tenofovir in that particular trial.

**THOMAS COATES:** But we will have a head-to-head comparison for vaginal and rectal exposure?

**LYNN PAXTON:** Yes.

**JEREMY SUGARMAN:** You mentioned that you're using this model of government-to-government collaborations in science. How does that comport with the Thai war on drugs and how are participants being protected?

**LYNN PAXTON:** Well, Thailand, obviously is a sovereign government. So we can advise, but we do not control what they do. We are very aware of the Thai war on drugs and of things that were happening during that time. That has actually backed off in the last few years. What we have done specifically within the trial is consulted with the police, and we've come to agreements with them about reducing any possibility of harassment for participants simply for participating in the trial. There's a working group that's going on right now that's made up of representatives from the Thai and U.S. collaboration based at our CDC field site and the Ministry of Health and including representatives from the judicial services to examine other things such as provision of needle exchange services and again to reduce the possibilities of harassment at these sites. And so we feel we've made in-roads. None of our participants have reported being harassed at the sites. We feel that at this point it is more of a theoretical concern; it's actually not really happening. Our participants have not reported any problems stemming from this.

**MITCHELL WARREN:** You mentioned the Thai enrollment figures, and I was curious -- in Botswana you said that you're anticipating 1,200. How far along were you before you went into hiatus?

**LYNN PAXTON:** When we made the decision, we had 33 people that were actively enrolled, and so by the time we finally called it off, there were a certain number of people who were sort of "circling". They had been through a couple of screening visits in the early enrollment, and so we went ahead and allowed them to enroll. So by the time that we finally stopped there were about 70 people in the current tenofovir study.

**MITCHELL WARREN:** And they will switch over you said?

**LYNN PAXTON:** They'll switch over. Obviously, they're going to need to re-consent; so anybody who doesn't want to continue will stop, but we assume they will want to continue.

**KIMBERLY PAGE-SHAFER:** Regarding the Thai trial, how are you handling and what are the rates of incarceration that are happening in this population? Because they do have high rates, and those rates are associated with seroconversion and more significant adverse effects of that in the vaccine trials.

**LYNN PAXTON:** Right. Well, we struggled about this for a long time, and we actually went ahead and requested permission to follow patients while they were incarcerated, and so that is what we're doing now. Since we made the decision to increase the time of follow-up and not have to come off after 12 months, we now have to decide what are we going to do to re-consent people who might be incarcerated at that time to continue in the study.

**ROBERT BOLAN:** Are there any plans to do resistance testing on people who get infected?

**LYNN PAXTON:** Absolutely.

**MELANIE THOMPSON:** Lynn, could you talk a bit about challenges to enrollment in Botswana? Because you have a 15-month projected enrollment period, but fairly low enrollment in the first six months. What's different about Botswana? What were the challenges there?

**LYNN PAXTON:** The main challenge I would say is that -- we're not a new field station, but the HIV prevention research part is new for this station. So in fact, we had to build clinics from scratch. We had to hire all the people, and so basically, I think we decided that we're going to go into it slowly to make sure that we're doing it well. The second thing is that we're working with newer recruitment methods for us, and so we're still testing out what works well and to a certain extent this hiatus has been actually good for us because we were able to look at what happened during the first three months that we were doing that and how could that be improved upon. We suspect that when we start up again that we will probably have a much faster recruitment than we did in the very beginning because we have learned from what we started off doing.

**JULIE DAVIDS:** I'm wondering if you've had conversations with the Thai community advisory boards and community partners about the decision to stay on the one drug while other trials switch over, and what their reactions and questions have been.

My second question is, in the initial planning of doing trials on injection drug users, what other sites/parts of the world were considered?

**LYNN PAXTON:** I'm actually not certain. I'd have to refer back to our local collaborators to what the actual comments were about that. We were looking more intensely at whether or not to switch over in the Botswana trial because of the logistics of where we were in terms of enrollment. With the Thai trial, we were very cognizant of a number of things, one of which is that if we were to switch over at that time, that would clearly put us at least a year and a half farther away from getting a preliminary answer as to whether or not this concept would work.

Regarding your question about what other sites did we consider for injection drug users, the Thai site, because of the fact that we have been working there for a long period time and we had an established cohort was really our one option. The other sites that we work in, are mainly in Africa, where there is not really much of an injection drug use problem. It's not to the extent that

there is in Asia. And in the United States, again, we didn't have the same sort of established cohort as we had in Thailand.

**JOHN COHEN:** Are there plans underway to challenge the monkeys off drug that were given Truvada and repeatedly challenged?

**LYNN PAXTON:** Yes. We've actually challenged some of them, and they got infected, so it doesn't seem like being on chemoprophylaxis conferred any long-lasting immunity.

**JOHN MORTIMER:** Is this a daily observed therapy?

**LYNN PAXTON:** In Thailand about half of the people are observed daily because we're working out of methadone clinics. So they come in and get their methadone and they get their tenofovir. In the other sites there is no observed therapy.

**JOHN MORTIMER:** Domestically there have been reports of a secondary underground market for tenofovir, where it's being resold by patients for whom it is prescribed, and I am concerned about a secondary underground market for study participants.

**LYNN PAXTON:** Well, I think that Susan Buchbinder is going to be talking about the actual surveys that were done about clandestine PrEP use. I am not personally aware of these underground markets, but that is always something that we're going to have to consider, particularly once we move into possible implementation status.

**THOMAS COATES:** I'd like to share a couple of reflections that I have that we'll come back to and which may enter into some of the discussions this afternoon. I was struck by a few things that the two presentations together brought to mind. One is the extensive communications -- as Bob mentioned, 26 months of communications to make sure that there was lots of involvement and also the varying perspectives from different groups of people. I know that those communications can be difficult and that may factor into some of our thinking about -- if there is an effort to make this a standard of care, what kind of communication efforts need to be engaged in with the communities?

The other issue that came to mind is the issue of research. We really need to think about what kind of postmarketing studies are going to be needed to really understand how this works.

I think there's also quite a high likelihood that we'll end up with a situation of uncertainty, and it could be much like the situation that we have with postexposure prophylaxis, where there was an attempt to do a randomized controlled study in the occupational setting, and people said, "No, thank you -- give me the drug, I'll take my chances." We have a nested case control study for occupational postexposure prophylaxis, and we hope that some of those statistics can apply to nonoccupational protection, but we really don't know, and it's quite possible that we may end up in a similar situation for PrEP. Bob said, "Well, it's not going to be possible to do a head-to-head comparison of Truvada and tenofovir alone. We certainly can't do a three-arm study. We probably can't even do a two-arm." So we may end up with some uncertainties, that is a real possibility.

I was also struck when you described the Botswana studies, in which we have half men and half women -- it may be the case that the protection could be different when the exposure is vaginal versus penile. We may be left with some of those uncertainties, and so we may be moving forward to an era where it's going to be difficult to have certainty, and that may become the case in prevention trials. I guess the other thing that sort factors into my thinking, as we're all well

aware, is that the NIH budget is severely constrained, and they're going to have to make some difficult decisions about how to spend their precious resources. And it's really prevention resources supported by the Public Health Service and the Gates Foundation and a few other groups. And so the questions will be "How many of these kinds of prevention trials can we afford?", and "Will it be possible to do these kinds of pristine, randomized prevention trials?, and "Do we have to consider other trial designs or other surveys or postmarketing surveys?" You talked about the Forum for Collaborative HIV Research and how they're thinking about combination prevention. We may be stuck with other kinds of evidence upon which to base our decisions, so that may be something we factor into our thinking this afternoon.

### **PRESENTATION BY SUSAN BUCHBINDER, MD**

#### *A Tale of Two Studies: The U.S. MSM Tenofovir Safety Trial and the San Francisco PrEP Survey*

**SUSAN BUCHBINDER:** I'm going to talk about two studies. One is the CDC-sponsored U.S. trial of tenofovir, and I have my colleagues -- Melanie Thompson from ARCA (Atlanta) and Al Liu from the San Francisco Department of Public Health -- who are working on that project. And I'm going to talk a bit about Al's PrEP survey in San Francisco.

I'm going start by talking a bit about why we're studying PrEP in men who have sex with men and what the issues may be in that population. Throughout the Americas, and in particular in South America, MSM prevalence rates are in the 15- to 30-percent range. We have a very serious and very concentrated epidemic in MSM throughout the Americas and in major urban centers worldwide.

The majority of HIV infections worldwide are in sub-Saharan Africa and in Asia, and the majority of those infections are occurring in heterosexuals. So why should we look at MSM? This question came up early on when it looked like there were a lot of PrEP studies going on in Africa and Asia in heterosexuals, and the question was "Is it good enough to apply safety and efficacy data from these populations to MSM or not?" The treatment effects might be quite a bit different in MSM than in heterosexuals or injection drug users for a number of reasons, including potential differences in drug uptake by the target cells of infection and the timing of viral dissemination by various routes of transmission, adherence patterns in different populations, frequency and number of partners and partner change, issues of trauma through sexual activity, etc. The potential for behavioral disinhibition may be quite a bit different in MSM than in other populations. And I don't think we really know how recreational drugs might impact on PrEP efficacy.

If you look at individual-level interventions for high-risk negatives, there are interventions that are timed to occur at the time of high-risk behavior and those that are not tied to the timing of high-risk behaviors. For those timed to behavior, we can look at a wide variety of behavioral interventions and harm reduction strategies, including physical and chemical barriers (eg, condom use and microbicides), and postexposure prophylaxis. All of these are interventions that are trying to intervene at the time of sexual exposure. There are also a variety of strategies that don't need to be timed to the risk behavior – interventions such as vaccines, treatment of STDs (eg, herpes suppression), treatment of substance abuse, and pre-exposure prophylaxis.

Behavioral interventions are the cornerstone of all of our biomedical prevention strategies, but we're going to need additional interventions that are not tied to behavior. This is in part why I think that's the case (*referring to slide*) -- we followed a group of 4,300 high-risk individuals in

eight U.S. cities over time, and some of them became infected. In these cases, we did a full calendar-based inventory of risk behavior and asked, "From the period starting three months before your last negative all the way through to your first positive test, tell us about every risk exposure you had with either an HIV-positive or HIV-unknown sex partner." At that time, we didn't even ask about negatives because we didn't understand what we later learned, which was that some substantial proportion of infections -- maybe upwards of 25 percent -- were actually people who were getting infected by people who they thought were HIV negative.

That said, each of these horizontal lines represent a single seroconverter, and each dot represents an unprotected anal or oral sex exposure to an HIV-positive or HIV-unknown sex partner during that week. If you ask people, "When do you think you got infected?" they might say one particular episode. But you can see that the vast majority of seroconverters had multiple risks over time. There are a few people who had a single isolated week of risk, but most people were having multiple risks over time. And when we do these interviews and talk to people, oftentimes they don't recognize that they were at risk during those periods. They think "Well, I really don't think that that guy was risky because..." and (fill in the blank) -- "he was too good looking" or "he didn't look like he was infected", or "we didn't really do anything that was as risky as any of the other things I've done." So we're going to need efficacious interventions that are not tied to self-recognition of the risky episode.

Now I'm going to talk a bit about the CDC-sponsored U.S. tenofovir safety trial otherwise known as Project T (in San Francisco) or The T (in Atlanta). There are two primary objectives. One is to look at clinical safety and tolerability, and the second is to look at behavioral safety. The reason to study behavior seriously at this time is that it's our best case scenario -- meaning, if we see substantial behavioral disinhibition in the context of clinical trials, given all of the counseling that we do, we've got a serious uphill battle ahead of us should we ever need to implement this at a population level. The secondary objectives of the study are to describe the number and resistance characteristics of intercurrent HIV infections, assess the social and behavioral impact of trial participation, and evaluate participant adherence to daily TDF.

We're enrolling 400 men who have sex with men at the AIDS Research Consortium of Atlanta and the San Francisco Department of Public Health. Every participant gets risk-reduction counseling, condoms, and linkages to prevention programs. Half of the group is getting daily oral tenofovir, half are getting a placebo. We have early safety visits and then quarterly visits for 24 months. So it's different than in the other trials you've heard about this morning -- this is an extended safety study. We get two years to follow up on everyone, and that's good because we'll also be able to add to the data that's coming in from all of these trials about longer periods of tenofovir use, and we're shooting for a diverse cohort.

Men are 18 to 60 years of age. They have to be willing and able to give informed consent. We're not looking for the riskiest men in this trial -- this is a safety trial. We're also looking for people who are basically healthy. There are a number of exclusion criteria; because again it's a safety trial we're taking people who don't have underlying chronic diseases. We're doing a lot of biomedical safety monitoring, and evaluating tolerability, clinical adverse events, laboratory studies, and in San Francisco we're also looking at bone density and total body fat distribution through DEXA scans.

We wanted to really look at behavior closely, as there have been concerns in the community that PrEP could lead to behavioral disinhibition. As others have shown, even modest degrees of behavioral disinhibition could overwhelm biomedical efficacy. We know that risk behaviors are often under-reported and difficult to measure. We also think that it's difficult to compare behavioral risks just in the two arms of the trial if everyone gets a pill from the same starting

point. People don't know what it is that they're getting, and we know that in all of our trials, risk behaviors go down. We think that real risk behavior goes down, but certainly reported risk goes down in virtually every trial that we do. Participants are being counseled and there are a number of other cohort effects. As Lynn points out, this trial is the best-case scenario; this is probably not what will happen in the community. Our study is a placebo-controlled trial in which half of the people start the study drug immediately, and half wait nine months. Within each group (immediately vs. delayed drug), half get tenofovir and half get placebo. So half are getting a pill immediately and half are waiting to get a pill, and that way we can compare behaviors in people who are getting a pill to people who are not getting a pill, as well as compare side effects in people who get tenofovir to the people who get placebo. The whole schema of risk behavior may change dramatically once efficacy data is available and knowledge about that is out in the community.

To get the most accurate risk behavior assessment that we can, we're relying on ACASI. There are limitations to every method of measuring risk -- we don't have an equivalent of MEMS Caps for body parts (to figure out what's really being done in terms of risk). We're collecting information through ACASI both on HIV sexual risk and recreational drug use, as well as some other issues -- depression, motivation for study participation, and issues of perceptions of efficacy and treatment assignment in the study volunteers. We are measuring adherence in three different ways. One is MEMS Caps, which are these little computer chips in the top of the pill bottle so that we can find out every time the pill bottle is opened and closed. We're supplementing that with pill counts and self-reported adherence. Participants will also be asked to report how often they may have misused the MEMS Caps -- you know, opened bottles but not actually taken pills out. We'll be looking at reasons for nonadherence using standardized questionnaires, and asking questions about medication sharing.

We have a variety of things we're doing on the intercurrent infections. We're assessing for intercurrent infections throughout, but also among the seroconverters we're looking at clinical symptoms, CD4/viral load, and genotypic and phenotypic resistance. We're also linking HIV-positive participants with care.

We're anticipating that we'll complete trial recruitment sometime in 2007, and we'll have a two-year follow-up period after that. We anticipated that there were going to be substantial community concerns, and we worked very hard from the beginning and continue to work very hard with community-based organizations. They've been instrumental in helping us think about what the critical issues are for the community. We also anticipated that people would not want to be put into the delayed arm. We were concerned that, with this wait-list control, what could the motivation be for the people in the delayed arm? And we found out that we were completely wrong about that -- some participants actually wanted to be randomized to the delayed arm! So while there has been a lot of concern and questions about whether people in the community are going to be using PrEP through the underground and finding their own sources and taking this all the time, what we hadn't anticipated is that people are really scared about taking HIV meds.

When we go into the community, first of all, people don't have any idea what PrEP is, so it's a really complex study to explain in the field. Our experience from our recruiters is they go into the field and people say, "What are you talking about?" and "Why would I ever want to take HIV meds if I don't have to?" There's a lot more resistance to taking HIV meds than we anticipated.

Recruitment has also been a challenge because the way people meet partners now is very different than previously. Five years ago, we went to clubs and bars and we had tons of people going there, and now people are using the Internet more and hooking up in different ways. This means that we need innovative recruitment strategies, and to get the IRBs to move along with

that. Developing new strategies for recruitment is challenging and takes time. Both Atlanta and San Francisco are recruiting through a variety of strategies. We do conduct traditional outreach and we work with CBOs, but are increasingly moving to Internet advertising with banner ads and working with TV, radio, and press releases. We also need to motivate our staff, so most recently we have used our superheroes (*referring to slide showing study recruiters in the community dressed in superhero costumes*). Previously, we had a campaign -- the Healthy Penis Campaign in San Francisco -- in which a person dressed in a six-foot penis costume does recruitment, and people would stop to talk and have their pictures taken with the penis. Since that campaign is over, our recruiters are now dressed up as superheroes "fighting HIV" and people stop to talk to them.

I'm now going to shift to describing our PrEP survey, which is a separate study. There have been a number of reports of PrEP use in the community. Jon Cohen did a nice piece in the *New York Times Magazine*. Daniel Costello did a piece in the *Los Angeles Times*. This issue has gotten picked up now by a number of sources trying to figure out the extent to which PrEP is being used. But we actually know very little about the extent to which PrEP is being used in the community. The one piece of data that's been presented publicly so far comes from CDC's survey at minority Gay Pride events -- five in four cities in 2004. Basically they used a self-administered questionnaire to ask whether people had heard of PrEP and whether or not they had used PrEP. From our experience, people get PEP and PrEP get very confused, and it's very difficult to know whether people really understand this distinction. So we can't be completely sure about the data, but these are the data that we have so far. They got almost a 50-percent response rate, which I think is phenomenal at a Gay Pride event, and it was a diverse cohort. I think that they're doing some data cleanup now, because there were some people who reported using PrEP who reported they never heard of PrEP. So again there may have been some confusion in the questionnaire. About a quarter of the individuals surveyed said that they had heard of PrEP, and 7 percent said they had used PrEP, and we don't really know whether or not that's the case. I think CDC is planning to do another series of interviews.

In San Francisco, Albert Liu is the PI of a UARP-funded study to look at PrEP use in the community, and we're doing it in two ways. One is a population-based survey of 400 men who have sex with men. The other is a higher-risk group of men who are attending circuit parties.

It's a random sample of people attending these venues -- not just sex clubs and bars or parties; they do involve Pride events and gyms and retail businesses and street locations, so it's a wide variety. It is sampling men who are attending places where you might find other MSM. It's not sampling so much people who may be less gay identified and may not be attending those kinds of venues.

Questions are being asked about demographics, where people are meeting other people (specifically meeting sex partners), other kinds of harm reduction strategies, information both about PEP use/knowledge and PrEP use/knowledge.

We can't do ACASI in the field, so we're doing the next best thing. We're doing surveys using handheld computers. They are interviewer-administered, so we'll get away from some of the self-administered problems, such as people not filling in or understanding the questions adequately. There are also built-in error checks so that you can't give incomplete or internally inconsistent results, and there are range checks and so forth.

There are a number of other PrEP surveys that are also taking place in San Francisco, and we've been coordinating questions so that we'll be able to compare our studies. The Stop AIDS Project is doing a convenience-based sample, and they've been doing these surveys over time so

hopefully we'll be able to track PrEP use. It's going to be really important to see what happens to PrEP use and risk behaviors after efficacy data are shared, particularly if they're positive, but also if they're negative. The STD clinic is also asking about PrEP use in a high-risk population.

When results come out for any of the PrEP trials, it may affect the other studies. I think it's plausible and perhaps probable that other efficacy data will be coming out before or simultaneously with our trial. There are lots of different things that we need to take into consideration -- not just low, medium, and high efficacy, but all the complexity around estimating actual levels of efficacy, as well as issues of resistance, adherence, and risk behavior, and how would those help inform what we think about what's actually happening. The timing of the results coming out from each of the trials is going to affect each of the other trials. There is often a difference between what we investigators and clinicians think, compared with what the community thinks. We may think that the results from one or more trials are not conclusive enough and that we need to do additional randomized controlled trials, but the community may not think that, and ultimately the community decides what trials are going to be moved forward and what aren't. So in the same way that you can never do an RCT of PEP, we may get stuck with PrEP before having enough information to make sound recommendations.

The study that's closest to what we're doing in the U.S. is the Peru study because it's being done in MSM, although they are using Truvada. Truvada is also being used with heterosexuals in Botswana. Remember that we're not just interested in efficacy in a single population; we're also going to want to know something about what would efficacy be like in various subgroups, and we hope we'll have the ability to do meta-analyses. We'll also be doing two kinds of exploratory analyses. One I liken to the "correlates of protection" analyses done in vaccine trials. In PrEP, we'll evaluate two subgroups of participants who took the active study drug and compare those who became infected with those who didn't. This may help us to understand what led to protection (eg, adherence, type of exposure, etc). Another type of analysis is parallel to a "sieve analysis" from vaccine trials where the groups being compared are the people who became infected on drugs versus the people who became infected off drugs to see if it looks like the drug was having any effect on the types of virus that cause infection, and the role of primary or secondary resistance. We're going to have very limited power to do these types of analyses, but I think we're going to need to coordinate these efforts across trials as best as we can.

We also need to prepare for the impact of results from trials whose results are released before our study is complete. For example, if you have very positive results from TDF in Thailand in injection drug users, should we move to providing tenofovir in MSM, removing the placebo arm? Would participants agree to a placebo control? Similarly, if the results from the Thai trial are negative, even if we think the mechanism of protection might be different, will MSM write off this approach and will they agree to continue in the trial, if already enrolled?

On the other hand, if we see very positive results using Truvada in MSM in Peru, would we be able to do a tenofovir study at all? Would we actually have to stop our current study and maybe use a tenofovir versus Truvada strategy to finish to the trial? If we see no efficacy using Truvada in MSM in Peru, I think we will have a difficult time continuing the US TDF trial.

We have to think about when all these results are likely to come out and how they might impact our study. There is a lot of contingency planning that we need to do. We know that PrEP knowledge is low in the community. We know that we're going to need to educate people about PrEP and what's going on with existing research, and put PrEP in the context of other trials. We'll need to do that in advance of the efficacy data coming out.

Thank you.

**MICHAEL ALLERTON:** How blind is blind in terms of a placebo-controlled study? In my informal community advisory board, also known as having dinner with my friends in the Castro, I've actually had people "Well, I don't know if I'm on the placebo or not." And then one person goes so far as to say, "Well, I know because I grind up my pill, taste it, and see if it tastes the same as my friend's prescription of tenofovir." So with that kind of strategy going on, how are you going to assess how blind is blind?

**SUSAN BUCHBINDER:** We're asking what people think they are on, so we'll be able to get a sense if people report accurately. We haven't done the blind taste test in San Francisco, but that's a good idea. We'll go ahead and do that. Some substantial proportion of people often thinks they know what they got, and they don't. The fortunate thing about using tenofovir in the study is that the side effect profile for tenofovir and placebo look very similar. So it may be very difficult to assess.

**MICHAEL ALLERTON:** My second concern is a bit more broad. There's still for me an elephant in the room here and that is -- and Lynn almost touched on it when she talked about changing the paradigm for looking at this as a prevention strategy similar to malaria -- how do you switch that paradigm in people's minds? The difficulty I'm having is that there's never been a social or political controversy about abstinence-only as malaria prevention. I've been dealing with the condom controversy for over 20 years; I was even sued by the Traditional Values Coalition once over advocating condoms. So in that sociopolitical context -- think about the HPV vaccine -- have you or any of the other presenters ever been presented with "No, that's not acceptable -- it's abstinence only"? Even with maximal efficacy, what's the acceptability rate or the next step forward with that sort of political consequence?

**SUSAN BUCHBINDER:** I think we have to maintain optimism, although I completely agree with you that we have this kind of reaction to HPV. There are people who think women should just die if they're going to be promiscuous, even though it may have nothing to do with promiscuity -- whatever that means. I think that the most similar controversy that we faced was around birth control pills. With the malaria analogy, people don't say, "Oh, goody. Now I'm not going to have to wear long sleeved shirts; I can go out and expose myself." But with oral contraception, there was also a lot of concern that it would fuel a sexual revolution. The thing that is a little disconcerting is that it kind of did, right? And yet we do have oral contraception widely available. I think we know that behavior change is important, and we know that we're going to need additional strategies. We know that abstinence isn't being practiced necessarily by the people who are making those statements. Ultimately we will find ways to implement effective prevention strategy, but first we need to know whether or not they're effective. With PrEP, I don't know how it's going to ultimately roll out. Maybe it will be used in certain high-risk populations for limited periods of time, or as people get into treatment programs -- similar to nicotine replacement -- while they're undergoing the behavior change. It's not a definite thing, but we need to know whether or not it will work and at the same time be anticipating how we would roll it out.

#### **PRESENTATION BY WARD CATES, MD**

##### *FHI's TDF Trials and Tribulations*

**WARD CATES:** Our study population was going to be 1,200 HIV-uninfected women from three countries -- 400 hundred per country -- and 500 HIV-uninfected heterosexual men in Malawi. The regimen was 300 milligrams of tenofovir, with the same secondary objectives that the others have talked about. What were the end points? Slightly less sophisticated end points, but still looking at the safety end points of liver, renal, and to some extent metabolism, as well as the

effectiveness end point measured by oral mucosal transudate (OMT) antibody and followed up by ELISA and/or Western blot. Something that got relatively little attention in the midst of the FHI efforts was that we had a formative protocol that Kate McQueen and her colleagues worked on. What was the objective of this? It was in terms of three aspects -- before, during, and after the trial. To look at the community response, qualitative focus groups and in-depth interviews were conducted. That was the pretrial. During the trial, the same type of qualitative methods looking at why people might have either declined or discontinued the trial, what was the situation in those who became infected, how acceptable was the oral medicine -- both to the individual participant and the community. And then after the trial, given what the findings were, how were we going to disseminate those findings and develop access programs (if effective), or explain negative results (if ineffective). All of this was protocol-driven and IRB approved.

What else did we do in order to try and prepare our West African and Malawi communities for these trials? Before we even entered the formative study, we had a formal Ministry of Health letter of support in each country, but don't forget that ministries of health change and political administrations can and did change in some of our countries. Our partners Gilead have been pioneering in terms of their public sector pricing. And our principal investigators in each of the three West African sites and in Malawi were selected based on their past experience with FHI studies -- both microbicide and/or contraceptive studies, and they had a track record of being trained with us. Again, well meaning, we thought we were hitting the ground running. We thought we were really in great shape, and we had lots of highs as we were going through this odyssey.

The formative studies were implemented in late 2003, the clinical trial training in West Africa in May 2004. At the Gates reception during the Bangkok AIDS meeting, one high point of my professional career was that I acted as the entry event for Richard Gere's talk where I was explaining the showcase prevention trial for the Gates Foundation. Then Tuesday there were four TDF formative posters, three from in-country behavioral science colleagues and one from Kate. So we thought we were really riding high. And there were even more highs after the Bangkok conference. In December 2004, Lynn Paxton held the CDC PrEP meeting -- by that time we had started in three countries. Our enrollment was on target, and preliminary incidence was very to answer the questions. In February the pretrial forum had worked again in Malawi, and in August the clinical protocol was approved by the IRBs.

So what were the lows? Well, there was the Bangkok Gilead demonstration protest in which Jim was nearly sprayed with red paint. The Cambodian trial was faulted in October 2004 and took a fair amount of our time. Then the Ghana government raised some questions as to two things. Number one, should we really be testing an antiretroviral drug because of the risk of resistance? And then, number two, should we really be dealing with sex workers given the U.S. Government position on this? Fortunately, we have some colleagues at FHI who are Ghanaian. They went over and spent several days with the Ghana government, answered the questions, and the study proceeded. In November, we came upon some operational irregularities at the Nigerian site having to do with storage of specimens, documentation, and informed consent.

By December 2004 in Cameroon, the "France 2" group, the equivalent to our "60 Minutes", was filming, and we sent over two members of our FHI team in order to assist them -- we didn't want them interviewing participants per se; it's not recommended by the FDA. It's probably not good to intervene, but we did help to find someone who was from the same community of participants, not an actual participant in the trial. Well meaning, we thought we would come out with a balanced program. In fact, on Martin Luther King Day 2005, the "France 2" program aired, and that became actually the precipitating event of some major activities within Cameroon.

In Nigeria we had put someone over there for a couple of months, and trained them to make sure they understood a lot of the laboratory issues and so on, but with continuing irregularities we stopped Nigeria again while we attended to those.

By February 2005, the Cameroon trial was suspended. By March 2005 we made a tough decision to halt the trial in Nigeria. In August 2005 the Cameroon trials was halted by FHI. In October 2005 the trial was halted in Malawi by the new Ministry of Health.

What happened as far as the seroconversions in these trials? We have 3 in Ghana, 10 in Cameroon (only 4 on product), and 1 in Nigeria. So we're dealing with lower than expected incidence. Our assumption was a rate of 83 percent TDF effectiveness in typical use. We were optimistic about 90 percent efficacy. Again, primarily a safety trial in many of these countries but we were really optimistic that there could have been an incidence rate of five per 100-person years in the placebo group (three per 100 person-years in pooled analysis). Thus, we were counting on 30 events, but didn't get near there.

In studies involving very sexually active women, we would hope that we would anticipate issues of pregnancy. We referred for contraceptive options, but in fact in all three settings we were getting rates between the 40's and the 60's of pregnancies per hundred person-years (leading several to speculate whether TDF was actually a fertility pill).

In Ghana there was a 35% probability of pregnancy at 12 months, with 2-3 months off product due to pregnancy. Ten percent of recorded follow-up is without product due to pregnancy, conferring the potential for a large effect on the power of ITT analyses and interpretation of results.

So that's the data from the FHI trials. The thing I ask always ask myself if why the public reaction to oral tenofovir? When you look at tenofovir versus acyclovir, there is a major public reaction to oral tenofovir, yet none to acyclovir (and no reaction for topical tenofovir). I know Yasmin Halima and others have addressed this in several of their writings, but it is an interesting issue as to why this particular approach to intervention has been so challenging.

What are the lessons? Well, you've seen them already in the three talks, and you've seen what we learned the hard way through the first tenofovir trials out of the gate: anticipate community reaction, especially with ART for prevention, formalize health care access, prepare communications plan, and identify credible local spokespersons.

In Malawi, we formed a partnership with the other research location in Blantyre, and we're planning tomorrow to re-appeal to the Ministry of Health; if this is effective we would like to move forward in Malawi substituting Truvada for tenofovir. If Malawi says no, we'll consider other sites, which we'll then bring to Gates.

Thank you.

**THOMAS COATES:** Thanks Ward. What is the status of information about the safety of tenofovir used in pregnancy? It's a category B drug -- it's not known to be harmful but it's also not known to be safe. I know there's interest in using tenofovir in pregnancy, and I just wanted to see what is the time line for having more information as to whether these women who became pregnant really needed to stop tenofovir. I agree with your protocol to stop tenofovir, given the lack of information. Going forward, could pregnant women today continue to take it?

**WARD CATES:** It's an excellent question. For tenofovir, the reproduction toxicology studies are very clean, and that's the basis for the category B -- both tenofovir and emtricitabine are category B. The limited clinical data doesn't suggest any specific problems.

**JON COHEN:** Was there any evidence of behavioral disinhibition in the women -- if they wanted to get pregnant and if they thought the drug was safe they might have unprotected sex with men.

**WARD CATES:** I just don't know what the answer to that, but I will make sure you get the answer to that question once we look at the data.

**JUDY CURRIER:** Chemoprophylaxis studies for prevention of opportunistic infections are fairly standard, but these studies have a different complexity to them because the risk (and adherence) may vary across the population. Has there been discussion about how the study should be analyzed so it could be more generalizable?

**WARD CATES:** I think there is consensus for the intent-to-treat analysis for all of these studies, and it's really the as-treated analysis where there's no consensus in how to approach that. I think it would be premature to suggest that there should be consensus -- there is much we still do not know.

**QUESTION:** Especially for the African studies, have you thought about what you're going to do about male circumcision?

**WARD CATES:** In the near future my belief is that if the two other trials show similar levels of effectiveness as the South Africa trial, it would be prevention standard of care to be offered -- certainly any males participating in clinical trials -- and the question that remains to be discussed within our group is do we then also offer it to male partners of women in certain trials?

**SHARI DWORKIN:** Could you flesh out some of the historical contextual issues that are relevant in some of these communities? Were there other relationships in place that gave you clues as to why the community reacted in certain way? Or were these new locations with tentative relationship? I'm coming from a perspective of being in a community collaboration, and I'm not totally clear as to how the histories of these contexts might have given some insight into what unfolded.

**WARD CATES:** We thought we were going to get really good systematic data by addressing the community of participants proactively. In Nigeria the trial was stopped for operational purposes, and one of the big post-trial qualitative findings was that people were really angry and disappointed. In Cameroon it was a whole different story. There were multiple communities that were involved, not just a community of participants, but the community media, the community of politician, a community of advocates representing the community of participants, etc.

**THOMAS COATES:** We heard excellent presentations rich in texture from the people involved in doing the research on this issue, as you obviously notice a lot of the research is outside of the United States. We want to look at it from a U.S. perspective, because there aren't going to be any large-scale efficacy trials here. We're going to have to use the information that is being generated in these other places that look at routes of transmission.

When we first thought about the next phase of the program, we defined it in terms of three these three possible scenarios -- high efficacy (say 50 percent or greater), mid-level efficacy (between 30 and 50 percent), and low efficacy (zero to 30 percent or perhaps even a negative finding).

Another scenario is that we're not going to have very clean information about this; it may be kind of murky. We're going to have to make our best guesses out of information that is less than perfect from a registrational clinical trials perspective. Each of the breakout groups will have to think about the imperfection of the data, because I think it's quite likely there will be inadequacies given the constellation of events.

What often happens in many prevention studies is a decline in incidence after the study starts, relative to the pre-study period. The studies are powered for high effect sizes and it's almost like they need a home run to prove efficacy. The comparison of males to females in Botswana and the so-called control group problem is that of course we can never fully anticipate all of the problems that are going to occur in this rapidly moving area, and one that we can think about and anticipate is what happens in male circumcision and what implications that might have for future prevention trials and the difficulty of funding and carrying them out in a way where one gets end results.

In addition to thinking about implications for research, prevention program funding, capacity building, media relations and communications, I put up another bullet that might be helpful for the breakout groups to think about, and that is community relations -- what kind of community relations are necessary to think about any kind of rollout?

Another thing that we'll need to deal with has to do with liability and labeling issues, which is something that should be thought about.

And then there is the whole issue of partners and do potential partners get offered this? How do they get offered this? How is it provided?

I also want to see if there are other things that people want to be sure to have discussed in the breakout groups.

**ROBERT BOLAN:** I'm an HIV clinician so I approach this whole idea from a clinician's standpoint. If you're going to use a formulation that has a combination of tenofovir and emtricitabine, you're using drugs to which the virus has different genetic barriers for resistance. Tenofovir's genetic barrier is very high, and it's not likely that if you have someone that takes a dose of it and then becomes infected that they're going to develop resistance to that drug. Emtricitabine, on the other hand, is different. It's like 3TC, and only requires one mutation -- M184 -- to render that drug ineffective, and it definitely happens fairly quickly on treatment. So the question is, in the populations being treated with this combination drug, if someone becomes infected, how likely is it that they are going to develop this M184 mutation? What's going to happen to that quasispecies of virus? Will it later become the dominant part of that person's infection? And finally, how likely is it that they may be able to transmit that M184 mutation to someone who they subsequently infect? I don't know the answers to any of those questions. I know that as a clinician treating somebody with HIV, I often look at the M184 mutation not as a harmful thing, but actually a helpful thing in that it decreases the replication capacity of the virus. In a population of folks that are newly infected, however, I think that the considerations are a little bit different. A related issue is the question of what might happen to people who are coinfecting with hepatitis B.

**SUSAN BUCHBINDER:** I think ultimately we don't want to be in a situation like we are with PEP, where we have very limited data. I was going to suggest that maybe we might think about framing the breakout groups differently. One scenario would be one in which all the trials look like they're heading towards a positive result, and have that group discuss how "positive" would positive need to be for different populations. One in which you'd say, "Things look not so good" and how bad would they have to be to rule it out. Let's say that you don't hit the mark for any of

these trials, but they're really calling for 80 percent efficacy. If you saw 40 percent efficacy, would you want to promote this and in what kind of situation? So if one could think about the scenarios one turning towards all positive, one all negative, and one sort of what happens when we have a mixed picture -- how do you proceed? I'm wondering if there's a way we could incorporate that kind of thinking. I just want to move away from thinking that we're going to know that it's 80 percent versus 40 percent effective, because we're not. I think we're going to be really uncertain.

**THOMAS COATES:** Okay. We'll divide the group into three and Group 1 will be all of the evidence pointing negative. Group 2 will be evidence pointing in different directions, and Group 3 all the evidence pointing in a positive direction. From the list of bullet points to think about, point 1 is what would the next set of research priorities be. The second area has to do with prevention programming -- where does PrEP fit in a comprehensive prevention approach in this evolving set of strategies. The third bullet has to do with funding, and it relates to the issue of cost and support for care and treatment, as well an issue that we're going to revisit tomorrow morning with Martin Shapiro's talk -- would it lead to a bifurcation by source of funding? The next bullet has to do with capacity within the community for clinician and prevention providers -- how is it that community providers who maybe don't have medical capacity can work with these kinds of strategies, and what kind of work needs to be done to help us get to that point. There is the issue of media relations and communications and this is the issue of community relations and how do we deal with that. Another issue that came up was the liability and labeling issues, and whether CDC will think about issuing guidelines as they did for postexposure prophylaxis. We'll also need to consider the implications for partners and how partners are reached and provided opportunities to participate in these kinds of strategies. Another issue that was brought up was that of comorbid conditions.

**BRENDA LEIN:** I would also address the potential impact of PrEP on prevention funding for research and the impact on vaccine research.

*[MEETING ADJOURNED FOR BREAKOUT GROUPS 1, 2, AND 3 TO CONVENE.]*

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## **DAY TWO PRESENTATIONS & DISCUSSION: FRIDAY MAY 12**

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### **REPORTBACK: OPTIMISTIC SCENARIO**

*Studies All Point in Efficacious Direction*

#### **AGNÈS FIAMMA:**

I am speaking on behalf of the high efficacy group, which I chaired with Bart Aoki. We first looked at some general issues and thought about what would be sort of a paradigm shift in prevention as a result of high efficacy and a good safety profile. We also looked at the impact that different safety profiles would have. We thought about what components would go into PrEP delivery, beyond just drug delivery or discussions.

We discussed about what the research priorities should be in the case of high efficacy. We thought the first thing would be very serious qualitative research along the lines of market

research, looking at acceptability and at current practice -- such as current level of use, patterns of use, intermittent use. We wanted to look at frequency of HIV testing in PrEP users. We also thought it was important to look at women's pregnancy goals. Active surveillance of PrEP failures was also a priority – getting rigorous data on what happens when people are taking PrEP, whether they are taking it intermittently or regularly, what happens? What are the failures? Are there any failures? And how do we want to characterize those and think about analyzing them?

Then we thought about prevention programming. We thought we would need to identify appropriate delivery mechanisms. We thought we would want to emphasize the need for a comprehensive package of prevention services, not just a prescription being written. That would require a suite of services, including adherence counseling, risk-reduction counseling, and close attention being paid to all of the sorts of needs that people would have, and establishing those services. We also thought this would go hand in hand with provision of mental health services. As I said, we were the optimistic group. Not all of those things are going to be realizable, though we thought we would want to have ideal scenarios.

We also considered that we would need to target very specific high-risk phases in life. Not just high-risk groups, but to think about people's risk being kind of a cyclical or example, young people moving to cities, coming out, and coming to terms with their gay identities might be specifically high-risk periods. PrEP may be a short-term, rather than life-long intervention that may benefit people. We thought about the policy implications of telling people we are going to give them PrEP for the rest of their lives and the implications on sexual license.

We really focused on the need for the prescription to include more than drugs. We thought about alternative methods of delivering these other components, such as videos, written materials, additional counseling around PrEP, and then general counseling around risk or mental health needs. We thought about who would deliver all of these services, and we thought about medical staff. That's actually going to be very tricky. Medical doctors can't really be in all of these places at once, so we are going to need to think about who we enlist and who is trained to do these things.

We had an interesting discussion about dosing schedule and dose levels, what is the minimum protective dose? What are the alternative delivery modes? What happens if people take PrEP intermittently, or take it occasionally? What things do we need to know about that and include in the programming and dissemination and guidelines? We concluded that there was a need to define a minimum package of care around PrEP, and a standard of prevention that this could be incorporated into.

Identifying appropriate high-risk groups for PrEP is quite a tricky undertaking. We think it's complicated by people not being terribly good at evaluating their own risks. We need to think about how to identify those groups and treat them appropriately. We thought we would need to provide clinicians with guidelines that would be very specific about risk assessment and deciding who should get PrEP; Michelle Roland shared with us a lot of the issues around giving PrEP inappropriately to low-risk people. We want to prevent that sort of scenario from arising.

We identified the need to reach hidden populations, such as non-gay identified MSM. Then we came to the slippery question of funding. We thought about the impact of using research money for PrEP; was it going to divert funds from other prevention strategies? Was it going to divert funds from treatment services?

We wanted to look at cost-effectiveness data more than the cost of popping pills en masse. But also thinking about the full range of services and about resistance and the issues around long-term

treatment of people who may have been on PrEP. Some of the things we would need to think about in terms of policy would be legislating against discrimination, of people taking PrEP, such as in the case of preexisting conditions.

We talked about product registration, which may be contingent on some form of indemnification against product liability and how that's going to interplay with the issues around insurance and Medicaid.

We need to build parallel or symmetrical kinds of advocacy around HIV prevention. And people in these prevention constituencies would need to advocate for research and implementation of technologies such as PrEP, similar to the way the treatment advocacy efforts have done so.

We thought stigma was going to be quite a problematic issue. The suggestion I really liked was putting PrEP in the same sort of packaging as birth control pills and so forth. There will be the need to find ways of packaging it so it doesn't convey, "I am an awful, promiscuous person", and to think about ways to reduce stigma in the actual delivery of the product. We wanted to address the issues of stigma around taking an HIV medicine. We thought HIV medicines themselves carry a certain burden of stigma. We need to think about that very carefully.

Then we spent some time thinking about the potential negative consequences of people taking PrEP in terms of hiding their medicine and the potential for domestic violence in couples. We need to think about those issues because they will definitely be relevant if this goes into an operational mode.

We also discussed media relations. We were very fortunate because we had a journalist in the room, who gave us all of the insights. He told us we could not, to our great dismay, tell the media what to do, which to all us bossy people came to a complete surprise. We got a lot of interesting insights in things we need to focus on. One of the things is to really cultivate media relationships, and do that on an ongoing basis and at the local level. Get into the ears of the people that we want to be talking to, so we can maintain an information flow. We need to think about messaging and controversy -- we have got to have conflict. It doesn't have to be negative. But what is looked for is things that are going to be newsworthy because they contain conflict. We think we need to be really proactive and anticipate the sorts of concerns and protests that people will come back with and really be prepared to address the issues. We agreed that this boils down to some of the things that Bob Grant was saying yesterday about the need for a very comprehensive community preparedness process. We came up with some recommendations around media. We thought it would be useful to convene a media-relations working group that would think deliberately about writing press releases, distributing materials and information to gay and local media, and briefing media, academic, and public relations people about the issues. They thought it would be nice to have a specific Web site with questions and answers to serve as a repository or central source, and to provide a bibliography of what is out there about PrEP. We then thought about what the guiding principles should be, if we are to engage the media. Is it premature? If you don't, you are going to be caught at the end of the day. You want to have a transparent process. One suggestion was to target science writers. Those are registered in national associations, so they are readily accessible.

Thanks to all of the breakout group participants for their very thoughtful and lively discussion.

**SUSAN BUCHBINDER:** I am wondering if there was any discussion about how good does "good" have to be to start doing the implementation?

**AGNÈS FIAMMA:** We did actually think we would need to define that. Is it 60 percent? Is it 90 percent? And as soon as we got into that discussion, we started diverging. But we thought that really good would have to be an ideal of 90 percent or something. If we were at 65 percent or lower, what would we need to think about? I think we decided to peg ourselves on the high end.

**SUSAN BUCHBINDER:** And how do you pitch the really good news but with some moderation, so there isn't a lot of behavioral disinhibition, or back off because they are in clinical trials?

**MONICA RUIZ:** In response to Susan's question about level, how good is good, we actually did have that discussion, and I think it falls into defining what PrEP is and what it isn't. But it is a very tricky issue, because people have various understandings on what efficacy is and different perceptions of what is good enough for them. A 50-50 chance, 50-50 level of efficacy may be fine for one person but absolutely not another. So I think that is going to have to factor into how it is explained to the general public.

**MELANIE THOMPSON:** I think we advocated for additional research, not just a qualitative framework, but in the context of carefully controlled clinical trials. You can argue about what the trials may be, but certainly two areas were looking at safety and people who have morbidities and impaired renal function that are not in trials. One concern is the altered dosing issue, so that could be looked at.

**AGNÈS FIAMMA:** I realize now I left off another thing, which was to look at what would happen in Phase IV. What happened when people started taking it -- who are healthy or not so healthy -- and a lot of people in clinical trials, what will happen then? That would be research that we need to identify.

**MELANIE THOMPSON:** Research in adolescents.

**THOMAS COATES:** I thought the suggestion and recommendation that came out for some type of well-funded active surveillance program for Phase IV dissemination, to find out the nature of the use and the consequences of that, would be helpful.

**JULIE DAVIDS:** It might be useful to have specific packaging that has its own identity. Bupropion used for quitting smoking (Zyban) has a different identity than the anti-depressant application (Wellbutrin). But I also want to say that there is not a collective "we" with regard to PrEP organizing. No matter what level we are at, whether it's making plans for what "we" need to be doing right now or to prepare for where "we" may be in five or ten years, I don't know who "we" is. There is no secretary, no central coordination. It's tremendously confusing from an outsider perspective. PrEP Watch is up there and needs to be built up. That's great -- I know who the "we" is for that. But as far as the research and resources, the "we," is much less clear.

**JAMES ROONEY:** You mentioned several different scenarios where PrEP could be used. Some may involve continuous daily dosing, but in other settings it may be used very briefly in advance of a high-risk exposure, or used for just a short period of time. I am wondering if you discussed whether the current studies have any bearing on the alternative setting, whether there was any policy recommendation to be made? Also, was there any need for additional research that might try to link what may be happening in the current controlled clinical studies with the perceived needs of how it's used in the community?

**AGNÈS FIAMMA:** We definitely agreed that current studies were not going to be sufficient to inform short dosing or dosing to address short-term high-risk episodes. We thought that was definitely a research need.

**JON COHEN:** I wanted to point out a Web site you might look at called Talk Origins. If you look at the FAQ, they bring up every intelligent design argument, every criticism of the theory of evolution and they deal with them. If you go through that and you still believe in intelligent design, you don't believe in science and information and logic. I think the anti-HIV community could be addressed that way as well. I do think you are going to run into the anti-HIV community, because when I wrote this *New York Times* magazine article, I was attacked. It was called "Jon Cohen's Bright Idea" on their Web page says. It's a dissident group -- the people who don't believe HIV causes AIDS. Their No. 1 argument is the drugs are toxic and horrible, and they are going to jump on this. The point I was making about controversy is to embrace it because conflict is a good thing. Science is all about ideas hitting each other. It's not a negative thing. And I think scientists, when they deal with the media, run for the hills for the idea that conflict isn't good and their press officers tell them to avoid conflict. It's a lie. Conflict is great. Embrace it. You live for conflict. Every paper in scientific publications is telling you something that says "Everything you have heard up to this point is a little bit off. I have got some new information." That is conflict.

**JOHN MORTIMER:** In thinking about which services comprise PrEP, to think about a continuum of services, that's not a one-size-fits-all.

**THOMAS COATES:** Right, it doesn't need to be one-size-fits-all. Different people may want to access different parts of things. An analogous discussion that is always brewing has to do with voluntary counseling and testing. Do people need pre-testing and post-counseling? Most people don't do it that way. Most people get in to a doctor's office and it's pretty quick and simple. There are different models and it is not one-size-fits-all. In terms of thinking of a clash of ideas and where we are in this epidemic, of course, is there is an AIDS industry. As they attempt to realign the tectonic plates of the clinical trials networks, they are in a totally unenviable position as there are a lot of vested interests that are dependent upon that. We have the same kind of revolution going on in prevention. I think male circumcision and PrEP and other strategies will revolutionize prevention and may disrupt certain streams of money and may disrupt certain agencies doing things. We have to be prepared for that, and again that discussion, so that either those agencies reinvent themselves or they go out of existence.

**JUDITH CURRIER:** I was wondering if your group talked about, in the high efficacy state, where is this going to be delivered and by whom? Because it does require a prescription -- you need somebody with a license to write it. And right now most prevention services are delivered in places that don't have people that do that. It really requires a marriage of the prevention and treatment communities to do this. Did you have any discussion about how it actually would be implemented?

**AGNÈS FIAMMA:** We did talk about how to get the bedfellows together. We didn't actually come up with a solution, except to think about needing to do that, and how difficult that would be. We need to come up with ways of getting people to a one-stop shop where they can access these things.

**THOMAS COATES:** A more radical solution may be, as has happened with HIV testing as oral testing and those things came about, is to move away from having it prescribed. Do we have it available in a different form or OTC or non-physicians being able to dispense it? This may be a way to shake up the system as well.

**MICHELLE ROLAND:** My sense about this is that it's going to be a very local issue. One of the principals that I would hope that we would all adopt is that you want to try to integrate new interventions into existing services that work well. And how each of those local communities is going to assess what their existing services are and how best to integrate this and how to best take advantage of the continuum of services and build in the new opportunities that we have. I really think it's going to be local, but going to depend on defining a core minimum services and accepting this principle and trying to integrate into existing services.

**THOMAS COATES:** So for example, one set of existing services might be STD services; another might be drug treatment services -- they do give out controlled substances.

**DAVID VAN DER GRIFF:** I didn't see anything about who pays.

**AGNÈS FIAMMA:** Didn't I say we were the optimist group? You know -- money grows on trees.

**DAVID VAN DER GRIFF:** I know you had the point about having legislation about preexisting conditions to deal with the private health insurance. That's certainly something that should be considered. And presumably if private health insurers do cover this, public insurance programs such as Medicaid would follow. Actually Medicaid would probably lead, I think. But then we don't even have a national health insurance system in this country or the state. I am thinking in terms of right now and folks who are relying on ADAP who are HIV infected. Then is there going to be a competition for that funding?

**AGNÈS FIAMMA:** This is not cheap, so it's a major consideration. We were thinking registration would certainly facilitate insurance uptake. We didn't actually resolve the issue of who would pay. We do need to think about the cost. We could arrive at all sorts of different delivery mechanisms. We could have a patch. We could all imagine these wonderful scenarios. And then we could give everyone a home testing kit and they could go home and test themselves every month with an oral test kit. We could come up with all kinds of things that I would imagine would be quite expensive. But we need to do a lot more to figure out how it's going to work, and how much it's going to cost, and who is going to pay for it.

**TOM COATES:** Thank you very much to the optimists.

### **REPORTBACK: PESSIMISTIC SCENARIO**

#### *Studies All Point in Non-Efficacious Direction*

**TRISH KARLIN:** Our group focused on low efficacy or also in some ways we were talking about the failures scenario -- if the group of studies points to this not working. We talked about the definition of failure. We talked about research, messaging, funding, and capacity building. I will go through each of those points.

Our conversation really started with how to define a negative outcome. There was discussion that the definition of negative outcome may evolve over time and may vary by population. We heard in the first presentation, "how good is good?" We talked about "how bad is bad?" We discussed that, if all went well in the trial (ie, everything being conducted perfectly), less than 40 percent efficacy could define failure.

From there we moved into a discussion of research, namely that a negative outcome would point to the need for more research to identify what went wrong and also what might be changed to

achieve a better outcome. If we do see a negative outcome, we would need to determine the reason for the failure. Aside from lack of efficacy, reasons could include adherence, resistance, tolerability, study conduct, safety, not meeting end points, study power, and study design. We felt it was important to emphasize that a failure for Truvada or tenofovir does not necessarily mean a failure for PrEP. There was as mention of microbicides and nonoxynol-9 as an example that research should move to identify second-line possibilities such as entry inhibitors.

We felt there was a need to plan now for meta-analyses to answer to begin looking at how we might pull data to answer the most pressing questions. There was discussion of DSMBs being networked in some way to address negative outcomes or to prepare for communication around negative outcomes. It may be important to organize a think tank to review the outcomes and also to carefully consider why primate data would be different, why we are seeing different results from these trials and from some of the primate studies. Was it the wrong challenge, a wrong design, or do differences in nonhuman primates reflect deficiencies in the model that have been seen in vaccine research? We also talked about studies adding exit interviews to address operational challenges in studies, and looking at qualitative data analysis.

We then moved on to messaging. Clear messages would need to be developed for all constituencies. We would need to be clear on what we need and also what we don't know, including the need for additional research. But information dissemination strategies need to be defined. This is similar across all of the groups that will be presented today in terms of outcomes. Needing to be organized and needing to be defined. We talked about the need for a PrEP network or even perhaps a broader prevention network to deliver messages. We talked about who receives the call when the bad outcome is identified. Who is that group? We talked about tiered messages, needing to be ready for each study that comes out. Thailand is likely to be first with the release of results, with preliminary data expected at the end of 2008. If the result was negative, we need further evaluation to avoid a possible premature reaction and also to adequately explain those results. You need to be clear on a negative outcome. The use of a drug for PrEP does not mean a negative outcome in the use of that drug in a treatment scenario. Timing is important. We think we could be facing major prevention announcements simultaneously with PrEP trials, microbicides, vaccines, and circumcision trials potentially reporting within a similar timeframe. Also, we need good messages on PrEP versus PEP. Failure for one does not mean failure for both. And finally, to really emphasize what works in prevention -- to not let a negative outcome on the PrEP trials take us down in a spiral on other prevention strategies.

We talked about key messages for funders. Again, research is critical. The messaging is key. We talked about the need for straightforward information; the AVAC brochures were cited as a good model. It's something we might look at in terms of how to better educate the funding community. Also, increased advocacy for new research and new trial sites or scale up of existing sites is one of the key issues. We talked about the need for funders to see networks and collaboration instead of competition. The collaboration and smarter study design may attract additional investments.

The last topic we discussed was capacity building and the importance of bridging the medical and non-medical prevention. There is a need to develop capacity to evaluate what is happening now in the community in terms of casual dosing. The physicians need to be prepared to talk to patients about casual dosing and party dosing. There is a need to boost research literacy in general, to strengthen networks, and to message to the community, to funders, and to patients. Community groups need to strengthen their capacity to counsel and address questions about PrEP, to develop capacity around messages of PrEP versus PEP, and to leverage capacity to attract people to trials.

How do we work together as several different studies are trying to? How do we maximize that message to get mere people into studies? Health departments were mentioned as a key consumer

in terms of need for information. We talked about the need for both consumer and provider fact sheets around PrEP and PEP.

**GEORGE AYALA:** The only other thing I would like to add was, I think there was a sentiment in our group that there was no reason for us to wait to act. That we could act now on a number of the recommendations, especially as they related to how we think about messaging to a variety of constituency and state groups. At the same time, we should be strategic and really careful in how we think about the messaging and the audiences that we are trying to reach.

**THOMAS COATES:** Thank you for a very good report. You made a good point that study failure should not lead to an abandonment of the strategy. Probably one of the best examples of that has been in the microbicide area. Nine studies were disappointing but we have groups that are very strong in microbicides, and there is great hope and excitement in that area. The other thing that is happening in microbicides, in addition to doing other trials, is they are learning it does come from a prevention approach. It needs to involve couples and all sorts of things. That's one example. The other example is the Rakai study where they did get a spot-on same level of incidence in the incident and control group, but were very clever looking at the data and came up with a number of very interesting insights. They are the ones who published the information about the relationship between viral load and risk of transmission. They are the ones who really spurred the more recent interest in male circumcision. They are the ones that spurred the interest in HSV as a main STI that may facilitate acquisition. I think there is plenty of precedent for us to think about. I also like the idea of thinking of a PrEP or prevention network that parallels what the first group said; that is making sure there is a group of people that is continuing to advocate for these issues and think about how to keep the field moving forward.

**MICHAEL ALLERTON:** One of the things that really struck me in our group was the disconnect between the different disciplines that would be involved in prevention. For example, a physician now is going to tell their patients "Don't try this at home." They are going to invoke "Do no harm" and "There is not enough evidence --don't do this." Whereas a treatment advocate would never say "Don't do this." They would say, "This is what we know. This is what we don't know. This is what the risks are." And they will look at individual autonomy and say, "The decision is up to you." But the concern of the treatment advocate was that they don't understand prevention as well -- they are not prevention specialists. If someone calls them wanting to avoid HIV infection, they can only talk about the treatment model. They don't have the capacity to do prevention education. Whereas the health educator may say "Well, why do you want to take PrEP? What are your risk behaviors?", and untreated depression may be the cause. You have three different disciplines all dealing with the same individual engaging in risk, which would have three very separate messages. So being able to build the capacity between them to understand those would be very important.

**JULIE DAVIDS:** I think a broader question underlies a lot of what we are talking about. If we anticipated that, in five to ten years, we could potentially have a broadened repertoire of prevention technology and methods, what should we be doing now with different stakeholders and audiences and with existing channels of communications and developing new ones to prepare for that.

**BRENDA LIEN:** One other thing came up that we felt might be addressed in the mixed-results group, but is worthy of mention. When we discuss "what is failure?", we might decide in the United States that failure is less than 40 percent efficacy, but in other countries where the trials are run a 30-percent efficacy may be adequate. And what would be the challenge faced if it's not available in the U.S.? As Jon Cohen suggests, we shouldn't avoid the conflict -- it's the story. I think that will be part of what we need to be prepared for. Then something not discussed, but I

think it always comes up, is that what could be happening now is a paper developed that defines key components of a comprehensive prevention program that includes components like PEP which that could happen already, and PrEP. It should also include broader-scale thinking about hepatitis B, hepatitis C, because it's the target audience.

**JON COHEN:** I haven't heard anyone discuss what happens if acyclovir works for HIV prevention by suppressing HSV-2. It's going to be a very similar scenario in terms of prescription requirements. If they both have data surface at similar times, I think you are all going to be faced with a very confusing scenario where you are trying to explain to people what these two different drugs are that are prescribed and how they are both preventative drugs, and both are confusing to the public and to patients

**DANA VAN GORDER:** It would be unfortunate to leave this meeting without a discussion and potentially some kind of consensus about the interim messages to folks. Should we try this at home? Should physicians be prescribing it to high-risk patients? We were talking very much about the future, but in this period of time before we have data, people are going to be making decisions about whether to try this.

**THOMAS COATES:** That's a good point. Let's definitely come back to that. The reason you stopped me in my tracks, Jon -- I am also thinking about the opposite scenario. There are not only the PrEP studies at stake. What if the whole group of prevention studies goes in the opposite direction and none of it works? What if acyclovir doesn't work? And if the other prevention strategies don't work? It will put a wet blanket on the entire field. We have to also be prepared for that. And again it may be the case that the mechanisms we are looking at are not the appropriate mechanisms. We may need to improve the strategies with the mechanisms, looking at other drugs that attack different parts of the life circle of the virus or other strategies.

**BOB REMIEN:** In terms of anticipating negative outcomes, the more we know about current practices and attitudes and beliefs about use of these medications, the better position we will be for drafting messages if there are any negative outcomes.

**MARY FANNING:** We need to start having a discussion in a broader sense about the prevention strategies that are out there and going on, to start thinking about these across the board. I know that's a bigger challenge. But there are themes that are being touched on in other ways by other groups, as though they are the only ones talking about them. For example, in the microbicide field people are talking about this whole risk benefit analysis being very different if you are looking at a high incidence population versus a low one. How could regulatory decisions be made in that sense?

**KIMBERLY PAGE-SHAFER:** Tom, perhaps you could address low efficacy issues that have come up with Project Explore. I think no one has abandoned the need for behavioral education approaches to prevention.

**THOMAS COATES:** There was something of an effect there, and yet the confidence interval for the relative reduction crossed zero. You couldn't be all that confident about it. You can see we had this profound effect in the first 12 months, but it sort of went away. Why did it go away? The control group caught up with the intervention group. It wasn't that the intervention regressed, it's that the control group caught up. If you look over time at what happens -- if you do VCT every six months, ultimately you end up with the same point. Trying to explain that to the public is very complicated.

**SUSAN BUCHBINDER:** I think it's important when things are a failure to pitch them as a failure. We need to try to be sure we understand as much as we can so we have a context in which to put the research results for ourselves. And then a context with which to explain it in the community so it's not just another piece of bad news, but it's really, "Here is what we are doing. Here is what we found. And here is where we are going next."

**LYNN PAXTON:** I think we are all in agreement about the need to work across prevention modalities. That hasn't gone unrecognized. Already, as I mentioned yesterday, the Forum for Collaborative HIV Research has started putting together a steering committee to start addressing that.

## **REPORTBACK: INTERMEDIATE SCENARIO**

### *Studies Point in Conflicting Directions*

**JEREMY SUGARMAN:** In term of research priorities, there are enormous questions. These are: Why are there disparities in research findings? We need to drill down on that in terms of biological, cultural, and behavioral questions. In terms of biological considerations, this is sort of Science 101. What was the drug administered? What was adherence like? What are the other drugs used? Recreational drugs? What is baseline immunity? And sort of again back to the selection bias question of "who are the people that are motivated enough to come into trials?" Finally, back to the behavior. What are the extent of exposures -- types of exposures and other preventative modalities that might be employed?

Switching gears, what about research priorities for us? That seemed so easy. That was the slam-dunk question for us. If the data are mixed data, let's go do more research. Everyone would say it -- and ironically, though, it sort of raises a couple of nice questions. We have to use the analysis that we talked about earlier, to say "What are the right set of research of questions? There may be considerations for the need for new animal models with non-naive animals. Then there is the issue of episodic versus continuous use. There are questions about pregnancy and breastfeeding.

With regard to prevention programming, you can't abandon other programming just because we have mixed results. The messages are going to be difficult. The messages are difficult with respect to PrEP itself. What is PrEP? How might it work? And then you have to add the confounding message that data that are mixed, which is going to be horrible to try to explain. There are going to be the obvious implications for personal responsibility. Whether people believe that or not, the message is going to be hard to counter. And delivery in different settings raises different opportunities and challenges. So there are going to be different prevention challenges in terms of clinical settings or STI clinics versus prevention settings, because of who is doing the job.

With regard to funding, mixed results are going to say, "Keep funding focused on research". Questions linger in terms of research priorities. Should we be looking at PrEP versus other methods of prevention? There are disparities in funding treatments. We are a vaccine-hungry culture, as our group pointed out. The debate that has been waging for about 20 years, about the notion of developing new message of prevention versus new methods of prevention, will be raised once again.

With capacity building, you have to think of all of the different venues - prevention versus STI clinics and clinicians at all levels. The whole notion here would be that there are missed opportunities to provide prevention management, whatever the prevention method is going to be, and the opportunity of the drug and the interest about PrEP does provide the missed opportunity.

If someone comes in and raises the question "Is PrEP right for me," that's an opportunity to provide prevention. On the other hand, clinics may not be familiar or now have adequate incentive in which to deliver the right kind of messages. What do we need? Education reimbursement. We already touched on the opposite issue -- providing a medical treatment within another prevention setting.

With media relations, it's going to be tough to communicate – there will be confusion. The science model – “sometimes it works, sometimes it doesn't” is not the sound bite you want.

There will also be liability concerns. We could think about the vaccine liability issues. With vaccines might be there is liability protection. We are thinking about how that might be implemented. We should be thinking now about liability concerns so that drugs can be labeled appropriately. If people know how to use them according to guidelines versus off-label use it may decrease liability for clinicians. For example, are there lessons from PEP? We have guidelines for using PEP. Guideline development can be important, especially when data are mixed.

An example someone posed yesterday in our group is, if you are working in an STI clinic, you have done all of the preventative messaging you know how to do. If a guy comes in with a second case of rectal gonorrhea, here is an indication where, although the data it is mixed, you may want to try this. Even if there consequences, there is not much left to try. You have tried everything else. How would you craft guidelines in that way?

We need to think about liabilities for institutions in which the work is being conducted. Nonprofit hospitals and the like are concerned about off-label use.

With stigma, the old hat implications for insurance and employability need to be seriously considered.

We need to identify and engage communities in the research process. Don't wait for the results here, especially when the results are mixed. And it sounds like the results might be mixed. If we are doing forecasting, now is the time to engage, not to wait. Don't set up communities for disappointment. Prepare for all of the scenarios. Engage the communities involved in questions now about those scenarios so they are prepared, regardless of how it turns out. Opinion leaders may be important. We need to look for and adopt best practices. One example is using a memorandum of understanding about what the communication is going to be like given certain results, to make things explicit.

There are ethical goals of what we are trying to accomplish. If we don't make those goals explicit, we won't know whether we are doing a good job with it. The four goals that we outlined were enhanced protection, enhanced benefits, legitimacy, and shared responsibility. Ways of protecting the participants were suggested by the community. The goal of saying "What can we do in the context of this research?" Other prevention programming, for example, is a way of enhancing benefits. Legitimacy – it has to be a legitimate exercise. It has to meet the standards of political legitimacy. If the trial is conducted in the community through appropriate engagement, there is shared responsibility; the research question is shared. So we can use this idea to advance a better understanding of community engagement.

Co-morbidity depends on the safety profile of PrEP. Obviously you will need to consider whether someone is HIV negative or positive before starting to use it. Screening for hepatitis B and creatinine levels may also be necessary. This may require medicalization of PrEP.

Thank you for your attention. That's our group.

**MICHAEL MONTGOMERY:** We have demonstrated, through our collective work with the manufacturers, that we can do a great deal to control the prices of medications. Maybe the time is now to start looking at how government needs to get together to prepare, to have some programs that can cost effectively produce medication for the purpose of PrEP.

**THOMAS COATES:** I might add, Michael is a Director of the California State Office of AIDS, and played a leading role with ADAP in helping to negotiate with the pharmaceutical companies for the group purchase for the state program. I would endorse it.

Before we move on to Martin's presentation on disparities, we would like to ask Michelle Roland to talk a bit about the findings from your study.

### **PRESENTATION BY MICHELLE ROLAND, MD**

#### *American Academy of HIV Medicine PrEP Survey*

**MICHELLE ROLAND:** I'll describe some preliminary information from an informal survey that the American Academy of HIV Medicine sent out to its membership a few weeks ago. This was a general survey covering lot of other things, as well as some PrEP questions. I am not sure how many people received it. The American Academy of HIV Medicine includes physicians, physician assistants, and nurse practitioners.

There were about 357 responses received. About 70 percent of the respondents were physicians. Eleven percent were nurse practitioners, and the remainder were physician assistants. These included family practitioners, internists, and infectious disease docs. Sixty-eight percent considered themselves to be HIV medicine specialists. It's a pretty experienced group of providers taking care of large patient panels, and being in practice really for many, many years. So that's kind of the context.

Two-hundred-thirty-seven people responded to the first PREP question -- 54 said they had patients doing PREP, 183 said no. In response to the question, "Do you think that PrEP works?" Nineteen percent said "Yes", eight percent said "No", and 73 percent said they were waiting for results of studies. People may not have understood the difference between PEP and PrEP, but 73 percent suggests to me they probably did understand what we are talking about.

The next question was: "Have you ever had a patient who took HIV medicines for PrEP"? And this is interesting -- 23 percent said "Yes" of 200 people who answered that question. And then if you have had patients who took PrEP, how do they obtain the medications? Forty-one percent say they wrote a prescription. Thirty-seven percent got it from a street source. This is scary. For what percent are using the following medications, 50 percent said nevirapine, and then of course tenofovir -- 82 percent. And then for your patients who tell you they have obtained medication for PrEP, what do you think are the main reasons? Twenty percent said patients use condoms but don't trust them. Seventy-five percent don't use condoms. Fifty percent are using methamphetamines. Thirty percent are using other substances. Fifteen percent say all of their friends are doing it. And three percent of respondents said they use PrEP themselves.

**THOMAS COATES:** That they had or would?

**MICHELLE ROLAND:** That they had. So that's the data that we have.

**SUSAN BUCHBINDER:** This is great data -- it's really helpful. And it is really complicated. The difference between PrEP and PEP, at least with providers, you have a better shot. One of the things that happened, I think, with the Minority Gay Pride Event data was I understand that some people said they had never heard of PrEP, but said they used it. We may need to look for any kind of internal consistencies to get a handle on the data. Seventy-three percent said they were awaiting results - maybe that's a more realistic group. It may be some people understood and some people didn't -- trying to figure out internal inconsistencies will be helpful.

**PRESENTATION BY MARTIN SHAPIRO, MD, PhD**

*Disparities in Care: Implications for Rollout of Pre-Exposure Prophylaxis*

**THOMAS COATES:** We focused this meeting deliberately on the domestic epidemic -- it's complicated enough. The domestic epidemic is a textured epidemic, and we need to keep in mind the constituencies that will need access to any kind of strategy, particularly prevention strategies. The people who may need this the most may be the ones that end up not having access to it. I thought we should conclude the meeting with a talk about disparities. Martin Shapiro is Chief of the Division of General Intern Medicine and Health Services Research here at UCLA and also directed the HCSUS study. I asked him to think about those data and other data, and then lead us into a discussion of that issue.

**MARTIN SHAPIRO:** Thank you, Tom. I was thinking about the comment about the guy who presents with a second episode of rectal gonorrhea. It seems very compelling if you want to do something for that individual and PrEP seems to make a lot of sense. Obviously the context in which he considers the strategy is the context in which you are trying to deal with the problem in a population as a whole. You have to think, "what is the situation of the population as a whole?" Which components of the population are likely to benefit from the strategy or perhaps be hurt by the strategy because of the extent to which resources or attention gets consumed in such activities?

I am going to talk about the HCSUS study, a national study of care for HIV disease. In thinking about it, we can look at the behavioral issues we are concerned with here -- a behavioral model for vulnerable populations that talks about what was involved in getting care and the outcomes of that care. There are a series of variables that are all relevant, predisposing characteristics of the individual that include demographics, socioeconomic status, sexual orientation, and life experience. This might include being homeless or having been in jail or being in jail. It also includes enabling characteristics, which could be your personal and community resources. It could be your competing needs -- to feed yourself, clothe yourself, and care for family members or others who are ill. It could be the availability, for example, of case management. Need characteristics would be perceived health -- health and evaluated health, which sometimes are quite different. Health behaviors include diet, exercise, self care, habits, risk behaviors, adherence and use of services. Thinking about adherence -- for example, we know if you give a prescription for ten days of a QID antibiotic to a group of people, about ten percent of them will take it just as directed. This varies by characteristics of populations. Then we come to outcomes. The outcomes obviously include health, economic, and social outcomes.

In the context of this meeting, there are obvious similarities between diabetes and HIV—both are chronic diseases that need good treatment over time. In diabetes you need eye exams; you need control of cardiac risk factors and glucose. Failure to receive treatment could lead to organ failure. In HIV, it's higher over a shorter period of time. Six months without treatment in someone who is immunocompromised could be lethal. Treatment for HIV requires monitoring for progression of the disease, which requires antiretroviral management and monitoring for organ

failure. We need strategies to prevent the spread of the disease and manage social and behavioral problems. Social and behavioral issues include housing, child care, home care, insurance, drug and alcohol problems, and many, many others. This makes me think we are moving in the same direction. Diabetes interventions with high-risk groups are clearly being advocated -- weight reduction, exercise, and interventions with medications

The HCSUS study was a nationally representative sample of people who provide HIV care in the U.S. The study began in 1996. People were sampled in the first two months of the year. Most of our research tends to be done in convenience samples. The problem with a convenience sample is that you don't know if your sample is biased -- you don't know the degree of the bias. You don't know whether your measurement reflects the measurement in that reference population. Probability sampling does allow you to, within a certain margin of error, represent the population well. So this was a three-stage probability sample in which we sample providers within communities. We had a good participation rate, getting data on at least 80 percent of our target population and actual interviews with 73 percent. We were able to weigh the data to represent the national population. What we concluded was that there were about 231,000 people known to have HIV who saw a doctor in the first two months of 1996. And there were about 335,000 in care, being defined as having seen a doctor within six months. That was certainly not much more than half of the population believed to be infected at that time. We know that these numbers have improved a bit. Treatment was obviously being revolutionized just as this study went into the field, so a somewhat larger proportion of the infected population is in care. PrEP is aimed at people who are not in care for HIV. About 90 percent of the population in care at that point had CD4 cell counts under 500. About 60 percent of the population had a diagnosis of AIDS. Obviously there were tremendous differences in the population even then, looking at the proportion of men versus women of different ethnicities. Even at that point, the majority of female infections were occurring in African American women in the country. This is relevant for thinking about any program of HIV treatment or prevention. There were large demographic differences in who was in care for HIV. In the west, the majority of the population was employed. In the northeast, it was 21 percent. This doesn't reflect the stage of the disease or demography of the disease. Many of the people who were not employed had never been employed.

In terms of where they were getting their care, about 60 percent of the population was getting care from providers of 50 to 250 patients, and 17 percent were getting care in larger settings. Only about three percent were getting care from providers with fewer than five patients. In terms of the kinds of insurance coverage that people had, 68 percent were uninsured or had public insurance (20 percent were uninsured), similar to the adult population of the United States. The 19 percent with primary Medi-Care insurance reflect people who had somewhat more advanced HIV disease. About one-third had private insurance. As the disease progressed, the proportion that were publicly insured went up, reflecting the fact that expenses for the disease have been and continue to be overwhelmingly in the public sector.

We looked at what we thought was good care, which was seeing a doctor once every three months, getting acute care in a doctor's office rather than an ER, avoiding unnecessary hospitalizations and taking meds, including antiretrovirals and prophylactics. You can see that even among patients who are in care, 15 to 16 percent weren't being seen as often as twice every six months. As many as 30 percent did not receive medications to prevent PCP even though the CD4 counts were under 200. In terms of protease inhibitors, which were introduced and generally available in December of 1995, by the end of 1996, 41 percent had still not received them. That improved a lot by 1998, but there was variability in the population in terms of how the phenomena played out. In terms of not having two visits in a six-month period, that was most common among the uninsured. That was also a population that used the emergency room more for their ambulatory care. In terms of hospitalizations, obviously those were more evident in the

Medi-Care and Medicaid populations. People with fewer years of education were more likely to be using the emergency room and more likely to be hospitalized. In terms of PCP prophylaxis, there was a fairly big difference, with the uninsured being less likely to receive it. The Medicaid insured were less likely to have received PI or NNRTI therapy by the end of 1996, compared to the previously insured. The Medicaid insured live more like the uninsured than the privately insured. Education plays out the same way with differences in rates of PCP prophylaxis and antiretroviral therapy.

If you look across these measures of access and distribution of care, compared to whites you can see that blacks in 1996 fared worse across the board, and Hispanics fared worse in four or five categories. By 1998 this had improved with protease inhibitors and ambulatory visits with Hispanics. If you look at women in 1996, they fared worse in three of five categories. There wasn't much difference by age in the population. If you look at women in 1998 compared to men, they were still worse in three out of five categories. In 1998 there are still differences, notably in protease inhibitor and ER use by insurance status.

Protease inhibitors and NNRTIs were a great triumph in HIV care. This is the portion of the population that had ever received those therapies. When you break it down by gender, there was a difference between men and women -- you can see the bars were not really getting closer together. When you look by ethnicity, the lines actually are a little bit closer together at the end than they were in the middle, but it does not look like they are going to converge. If you look by insurance status, again you see the Medicaid and uninsured very close together there at the bottom and clearly not having much prospect of getting too close to the privately insured.

So, that's what happens when a therapy for HIV diffuses in the population in the United States. That's part of the challenge that is faced here. There are other obvious characteristics of patients that vary a lot. Drug dependence is an example to give here that varies by income and varies by race and region. We looked at whether people had competing needs, and competing needs were substantial in all groups. They were somewhat higher in African American and Latinos than in whites. You can also see they were higher in people with lower incomes and people who were not insured.

There was a lot of unmet need for services -- benefits counseling, mental health care, housing, health, alcohol and drug services. Having unmet needs for benefits counseling and mental health services was greater among the uninsured. It was greater among those of lower income. It was lower if you had case management. In fact, case management not only decreased unmet needs but also was associated with a higher receipt of PI and NNRTI therapy and higher receipt of prophylaxis.

Things vary by state in this country. It is a vastly complex country to implement any kind of program. For the ADAP program, income threshold ranged from 125 percent to 400 percent of the federal poverty limit. Who will pay for PrEP?

We looked at the combination of uninsured or Medicaid insured in the northeast versus the south. There were more or less comparable proportions of the population who were in one of these two categories. But in the south, about three times as many of that subgroup were uninsured as they were in the north. So depending on where you are, you may or may not get the opportunity to receive these kinds of services.

HIV care varies by ethnicity, socioeconomic status, gender, and insurance status. ARVs diffused less rapidly to disadvantaged groups. A program to roll out PrEP would face enormous challenges in reaching the populations most in need of this care.

**JULIE DAVIDS:** I am wondering if there is related data on health disparity. There may be a way of looking at the implication from roll out from another direction as well. I know that for almost any kind of medical service you look at, there are socioeconomic disparities of who gets it. The more complex the service, the more likely there is to be disparity among the enabling characteristics for getting medical care. For example, is having a doctor -- if you think of the Latino population, many of them don't have sources of regular medical care.

**THOMAS COATES:** So the issue of complexity of medical care is an interesting one. One of the themes that came out of the working groups is the notion that PrEP is a complicated phenomenon. It's not just pills in mouths.

**KIMBERLY PAGE-SHAFER:** One thing that needs to be thought of in this context is the attractiveness of programs that could roll out in California that may not be available elsewhere, where we do have participants in our studies who have been put on a bus and sent to California because of their services.

**THOMAS COATES:** Which also goes back to another point, which is the service that research provides. A lot of research is focused on hard to reach or very needy populations.

So we wanted to then use this time for any concluding thoughts, comments, other issues you might want to put on the table

**BRENDA LIEN:** I think an important piece of these programs is that they be comprehensive and include hepatitis B vaccination and hepatitis C counseling. Those could be implemented now. Part of that is developing the outline for comprehensive programs. I really advocate the inclusion of other community issues and conditions.

**GEORGE AYALA:** I was really struck by the comments about enabling factors. It seems to me that one of the things we can consider doing right away is to comb literatures about enabling factors as a way for us to strategize, addressing disparities that we anticipate as related to PrEP.

**THOMAS COATES:** I think your point is entirely on the mark. They are known, so let's start thinking about them in a very concrete way.

**MONICA RUIZ:** If we are talking about strengthening the existing infrastructure of prevention to roll out something like PrEP, or a microbicide, or a vaccine, we need to make sure that we know how well those can be utilized, who those people are, who the programs are missing. And where those folks are going to get the information, if they are getting any at all. If they are getting any services at all, where are they getting them from? It might tip us off as to where we need to target the community or bring those organizations in to where we are talking about new infrastructure that might be able to roll out prevention interventions.

**JON COHEN:** Most things in science fail. I think that's really instructive. I think the likelihood of this failing is like everything else -- it probably will. Most things do. But there is something different about this. I have been following AIDS vaccine research for many years and monkey research. For the monkey data, if it were a vaccine, it would have people dancing in the street to have that level of protection. Like, this is different from anything seen with any AIDS vaccine that is moving forward. Obviously, this isn't a vaccine, but it does resemble a vaccine in many ways. And I think it is interesting, AVAC is taking this on. I encourage you to think creatively about what immunity is and how it works and how this does resemble a vaccine. I am not

suggesting people are going to take the drug, stop taking the drug and be protected the rest of their lives. That would be wonderful. I am suggesting there is a likelihood to learn about the protection if you look for it. There is only one trial I know who is doing it -- that is Bob Nixon. There should be 20 labs hungering to get at that data.

**SUSAN BUCHBINDER:** I think in scientific meetings we need to include some smart statisticians, who can also talk to us mere mortals who are around this table, to work through some of the issues.

**RENEE RIDZON:** For the Gates Foundation, I would like to go back to the point about looking across the prevention trials with regard to efficacy. This is something that has come up over and over again. And I think it's a very important topic. We are actually working towards doing some efforts for cross-prevention trials advocacy, realizing there are issues that are particular to each intervention. But there are many that are common. That commonality would be strengthened if we tried to work together.

**MELANIE THOMPSON:** I have been struck by the richness of the discussion of this Think Tank. I think there is an urgent need for some ongoing group to continue the conversations. Whether that group is this Think Tank structure or whether Gates sponsors it, or the Forum, doesn't really matter. Rather than having a lot of discontinuous sessions, it would be wonderful to have continuity. Someone described in our group yesterday this PrEP effort as disorganized. And I think it is. But I also think there is a lot of richness there. If we can harness it and come together as a group without the different turfs competing and so on, there would be so much that we can do. We really would like to advocate or have some structure for ongoing planned communication, rather than just have meetings here and there that don't add up to anything. We have a lot of work to do sooner rather than later, and terrific ideas that I hate to see vanish after this meeting or, you know, maybe get published, but not acted on.

**SHARI DWORKIN:** I think something that we can do immediately is to make sure we add post-trial qualitative debriefings to trials. Usually these are looked at as these open-ended silly things that simply get at issues that are under the radar in terms of adverse events. But I think we could probably use these as great opportunities to get feedback on issues of clarity of reception of messages, our social justice issues, and make sure that we are raising ethical standards as high as we can. And one thing that we have found at Columbia -- it is intriguing to sometimes use an interview external to the trial. That might be a consideration to ensure lack of bias in response.

**GEORGE AYALA:** I suggest that we think about parallel processes with other constituencies and stakeholder groups to carry the conversations more broadly. I worry about the people who are not here. I worry about how we might have conversations about the implications of successful PrEP trials in gay men of color and with organizations that serve those communities. I think we need to begin those conversations and engage in those constituencies now.

**MICHAEL ALLERTON:** I wanted to just springboard from something that Brenda said. I suppose I am looking for a greater context for all of this, and that is sexual health and improving the sexual health and well-being of people. Birth control was a huge step forward in sexual liberation, because sex without the fear of pregnancy was an advance. I think it was an advance; some people would dispute that. The next advance is sex without fear of disease. So to be able to integrate it with hepatitis B prevention and all of those things, I think that is the next phase in the context this should be put into. It would be great where the only hazard is a moral one and we are free to define the morality for ourselves. I think that's a piece that would be really important to look at as a broader picture as you are looking at prevention strategies.

**THOMAS COATES:** Another point that occurred to me is that the issue of “moral hazard” is really independent of administration. And different administrations bring their own moral hazard to the country. But they do seem to share the notion that we are a conservative nation with religious overlay. It is part of the reality in which we work, and it is something we need to take into consideration.

**JULIE DAVIDS:** I want to know how we would study or to what degree we would need or want to study different dosing.

**THOMAS COATES:** Dosing schedules -- amounts. Yes, I think it's a very important issue because these studies are large and expensive. It may not be possible then to lead an efficacy study. We may end up relying on less satisfactory information.

The other thing that occurs to me is the issue of sufficiency of evidence and alternative trial designs. We do like the satisfaction that clinical trials give in terms of the outcome and the clarity of the outcome, especially when the result is a good one. But we may be moving into a phase where that may not be an option for a variety of reasons. Both because the comparisons we are having to make are more subtle and refined, and because the resources won't be available. I think that's something that is a methodological thing that we actually may need to get engagement on as we move forward into the next generation of things.

With that, let me give you all our heartfelt thanks for being here, giving of your time, sharing your thoughts, sharing your wisdom. This of course is the 25<sup>th</sup> year of the epidemic; we can imagine where we will be 25 years from now. In the next five years, clearly, the challenge becomes more complicated as the field becomes more complicated. But the work is nonetheless important because of the worldwide epidemic. And hopefully what we are doing here makes a small but useful contribution to that. Thank you all for giving of your time and we will be in communication soon with the product of our thinking. Thank you all so much.

***MEETING CONCLUDED***

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