FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

THURSDAY, MAY 10, 2012

8:00 a.m. to 8:30 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

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C O N T E N T S

AGENDA ITEM	PAGE
Call to Order and Introduction of Committee	
Judith Feinberg, M.D., FACP, FIDSA	16
Conflict of Interest Statement	
Yvette Waples, Pharm.D.	21
Opening Remarks	
Debra Birnkrant, M.D.	25
Guest Speaker Presentation	
U.S. HIV Epidemiology and Risk	
Susan Buchbinder, M.D.	34
CDC Presentation	
CDC PrEP Studies	
Lynn Paxton, M.D., M.P.H.	53
Clarifying Questions from Committee	63
Sponsor Presentations – Gilead Sciences, Inc.	
Truvada Overview	
Andrew Cheng, M.D., Ph.D.	81
Pre-Exposure Prophylaxis (PrEP) Initiative	
Robert Grant, M.D., M.P.H.	92

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Antiretroviral PrEP for HIV-1 Prevention Among Heterosexual Men and Women: the Partners PrEP Study	
Connie Celum, M.D., M.P.H.	117
Jared Baeten, M.D., Ph.D.	122
Truvada for PrEP	
Andrew Cheng, M.D., Ph.D.	139
Closing Comments	
John Mellors, M.D.	143
Clarifying Questions from Committee	160
NIH Presentation	
VOICE Trial	
Jeanna Piper, M.D.	192
FDA Presentations	
Truvada: Pre-exposure Prophylaxis (PrEP) Indication for Prevention of Sexually Acquired HIV-1	
Peter Miele, M.D.	200

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Proposed Risk Evaluation and Mitigation Strategy (REMS) for Truvada for a Pre-exposure Prophylaxis (PrEP) Indication for Prevention of HIV-1 Infection	
Carolyn Yancey, M.D.	232
Clarifying Questions from the Committee	
Open Public Hearing	250
Clarifying Questions from the Committee	355
Charge to the Committee	
Debra Birnkrant, M.D.	438
Questions to the Committee and Committee Discussion	439
Adjournment	587

P R O C E E D I N G S

(8:03 a.m.)

DR. WAPLES: Good morning. I would first like to remind everyone to please silence your cell phones, BlackBerrys, and other devices if you have not done so. I would like to identify the FDA press contact, Stephanie Yao. If you are present, please stand. Thank you.

Call to Order

Introduction of Committee

DR. FEINBERG: Good morning, everyone. I'm Dr. Judith Feinberg. I'm the acting chair of the Antiviral Drugs Advisory Committee this morning. I will now call the meeting to order.

We'll go around the room and please introduce yourself. We'll start with the FDA and Dr. Edward Cox, and then go around the table.

DR. COX: Good morning. Ed Cox, director of the Office of Antimicrobial Products, CDER, FDA.

DR. BIRNKRANT: Debbie Birnkrant, director, Division of Antiviral Products, CDER, FDA.

DR. MURRAY: Jeff Murray, deputy director,

Division of Antiviral Products.

DR. MARCUS: Kendall Marcus, deputy director for safety, Division of Antiviral Products.

DR. MIELE: Peter Miele, medical officer, Antiviral Products.

DR. ESTRELLA: Michelle Estrella, assistant professor of medicine, Johns Hopkins, Division of Nephrology.

DR. HUNSICKER: Larry Hunsicker. I'm a clinical trialist and a kidney doctor from the University of Iowa.

MR. SHARP: Matt Sharp, PWA.

DR. VEGA: Buenos días. Good morning. Marlena Vega, patient advocate.

DR. WOOD: Lauren Wood, senior clinical investigator, National Cancer Institute.

DR. MORRATO: Elaine Morrato. I'm from the Colorado School of Public Health. I'm an epidemiologist in the Department of Health Systems Management and Policy.

DR. VAN DYKE: Russell Van Dyke, pediatric infectious diseases, Tulane University.

DR. MORRATO: Yoshi Murata, infectious diseases, University of Rochester.

DR. STRADER: Doris Strader, Division of Gastroenterology and Hepatology, Fletcher Allen, University of Vermont.

DR. GLEN: Jeffrey Glen, Division of Gastroenterology and Hepatology at Stanford University.

DR. DASKALAKIS: Demetre Daskalakis, infectious diseases, New York University School of Medicine.

MR. RAYMOND: Daniel Raymond, policy director, Harm Reduction Coalition.

DR. ELLENBERG: Susan Ellenberg, biostatistics, University of Pennsylvania.

DR. NEWCOMER: Susan Newcomer, demographer, National Institute for Child Health and Human Development.

DR. BLOWER: Sally Blower, director of Center for Biomedical Modeling, David Geffen School of Medicine at UCLA.

DR. CORBETT: Amanda Corbett, clinical

associate professor at the UNC Eshelman School of Pharmacy.

DR. GIORDANO: Good morning. I'm Tom Giordano. I'm an associate professor of medicine at Baylor College of Medicine in infectious diseases and health services research, and at the Houston Center for Health Services Research at the VA.

DR. KUHAR: I'm David Kuhar. I'm a medical officer at the Centers for Disease Control and Prevention.

DR. CHEEVER: Hello. I'm Laura Cheever. I'm the chief medical officer and deputy of the HIV/AIDS Bureau at the Health Resources and Services Administration.

DR. PADIAN: Nancy Padian, epidemiologist, School of Public Health, UC Berkeley.

DR. RUIZ: Monica Ruiz, visiting assistant professor at the Department of Prevention and Community Health, the George Washington University School of Public Health and Health Services.

DR. ROBINSON: Patrick Robinson. I'm

substituting as the nonvoting industry representative. I'm from Boehringer Ingelheim.

DR. FEINBERG: Thank you, everyone.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of the meeting with the

media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Now I'll pass it to Yvette Waples, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. WAPLES: The Food and Drug Administration, FDA, is convening today's meeting of the Antiviral Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 USC Section 208 and

Section 712 of the Federal Food, Drug & Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of at today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as

well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today the committee will discuss an efficacy supplement for new drug application NDA 21-752, Truvada, which is emtricitabine/tenofovir disoproxil fumarate, submitted by Gilead Sciences, Incorporated. The supplemental application proposes an indication for pre-exposure prophylaxis, PrEP, to reduce the risk of sexually acquired HIV-1 infection. A copy of this statement will be available for review at the registration table during this meeting, and will be included as part of the official transcript.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the products at issue.

With respect to FDA's invited industry representative, we would like to disclose that Patrick Robinson is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Robinson's role at this meeting is to represent industry in general and not any particular company. Dr. Robinson is employed by Boehringer Ingelheim Pharmaceuticals.

With regard to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. The following interest is being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Susan Buchbinder has acknowledged that she was the site principal investigator for the iPrEx study sponsored by the National Institutes of Health, NIH, and a PrEP study sponsored by the Centers for Disease Control and Prevention, CDC, for which Gilead Sciences provided the study drugs. She attended PrEP advisory meetings convened by Gilead Sciences, but declined receiving honoraria

or travel reimbursement. As guest speaker, Dr. Buchbinder will not participate in committee deliberations, nor will she vote.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firms at issue.

Thank you.

DR. FEINBERG: Okay. We will now proceed with the FDA opening remarks from Dr. Debra Birnkrant.

Opening Remarks – Debra Birnkrant

DR. BIRNKRANT: Good morning. I would like to welcome everyone to today's advisory committee on HIV prevention. Specifically, we will be

discussing Gilead Sciences' supplemental application for Truvada, emtricitabine/tenofovir disoproxil fumarate, for pre-exposure prophylaxis, or PrEP, in combination with comprehensive prevention strategies for HIV-1 prevention in populations at high risk of sexually acquired HIV infection.

(Pause.)

DR. BIRNKRANT: I also had a flat tire this morning.

(Laughter.)

DR. BIRNKRANT: The goals and approaches to HIV prevention were outlined in the National AIDS Strategy that was published in 2010. In this document, it states that: "We must move away from thinking that one approach to HIV prevention will work, whether it is condoms, pills, or information. Further, we must expand targeted efforts to prevent HIV infection using a combination of effective, evidence-based approaches."

Prevention of HIV acquisition with antiretrovirals is not a new concept. All we have

to do is look at the landmark paper that appeared in the New England Journal of Medicine in 1994 on reduction of maternal/infant transmission of HIV with zidovudine treatment conducted by the PACTG, where use of zidovudine was shown to significantly reduce maternal/infant transmission.

Where are we in 2012 with respect to the epidemic in general? Well, even with the multitude of approved products for treatment in six mechanistic classes, almost 150 PEPFAR-approved products, condom availability, and strategies to educate, test, and bring people into care, the HIV epidemic continues to affect millions worldwide. We have asked Dr. Susan Buchbinder to give a presentation on the epidemiology of HIV, but I'll share one key epi slide with you to place PrEP into perspective.

Although the number of diagnoses of HIV infection among adults and adolescents remains stable in the United States, for more than a decade, at about 50,000 per year, rates have increased substantially among MSM and particularly

among young minority MSM.

This slide presents the percentage distribution of diagnoses of HIV infection among adults and adolescents by transmission category from 2007 to 2010. The percentage of diagnoses on the Y axis shows that -- if you look at the top slide, the top line -- that there's been an increase in the category male-to-male sexual contact from 2007 to 2010, from 55 percent to 61 percent.

Why are we discussing this topic today? After all, Truvada was approved for treatment of HIV-1 infection in combination with other antiretrovirals in 2004, and the individual components were approved earlier, tenofovir in 2001 and emtricitabine in 2003. There are also interim CDC guidelines for Truvada for PrEP for high-risk MSM that were posted in 2011.

The supplemental application that Gilead Sciences submitted provides FDA an opportunity to extensively review and analyze scientific data, inspect clinical trial sites, and bring the review

and the data to a public forum for an evidence-based discussion.

What is PrEP? Pre-exposure prophylaxis, or PrEP, is the use of antiretroviral drugs to prevent acquisition of HIV in men and women in combination with other preventive modalities, such as condoms and counseling. We're focusing on Truvada today. The supplement received a 6-month priority review.

Under our Manual of Policies and Procedures, reviews are classified into either priority or standard. A priority review is a 6-month review clock, and standard review is a 10-month review clock. Priority review is granted if there is potential for providing significant improvement in the treatment, prevention, or diagnosis of a disease when compared to standard applications.

Truvada for PrEP was granted a priority review because there is a potential for providing significant improvement in prevention of HIV infection, and there is no other drug product on the market with an indication for HIV prevention.

We know that a two-drug combination cannot

be used to treat HIV. Resistance develops rapidly when fewer than three drugs are used at one time. Signature mutations for emtricitabine are M184V or I, and for tenofovir it's the K65R. These can lead to resistance and cross-resistance to other nucs in the class.

Why is this important? Resistance is a concern because Truvada is a key component of all first-line regimens, as outlined in the Department of Health and Human Services guidelines for the use of antiretroviral agents for HIV-1-infected adults and adolescents.

Clinical trials of oral PrEP are seen on this slide. Full data sets were submitted and reviewed from the studies highlighted in red, and include iPrEx, which was conducted in adult MSM at high risk; it also includes Partners PrEP; and it includes CDC TDF 4323.

Top line summaries of CDC's TDF2 and the trial FHI PrEP were also submitted and reviewed by FDA. Dr. Peter Miele will present FDA's risk/benefit analysis of the data. We have asked

Dr. Lynn Paxton to present the CDC trials, including the nonclinical rectal macaque challenge studies that served as proof of concept studies. We've also asked Dr. Jeanna Piper from the Division of AIDS at NIH to update us on the VOICE trial.

Gilead Sciences will have their consultants Dr. Robert Grant present the iPrEx data and Drs. Connie Celum and Jared Baeten present the Partners PrEP data. And Dr. John Mellors will address the potential for resistance development.

Dr. Carolyn Yancey of the FDA will present considerations for risk mitigation. Regarding risk mitigation, we need to be mindful that Truvada is already on the market for treatment in combination with other antiretrovirals, and it would be difficult to have two systems for dispensing the same drug. One system could be easily circumvented by accessing drug through a different system, and patients who are HIV-infected need to be able to access Truvada without restriction, as do those requiring PEP.

So in sum, prevention is a key goal in the

efforts to stem the HIV epidemic. In general, PrEP is viewed as another option in the prevention toolbox. It would allow for testing and bringing more people into treatment, and would reduce the risk of acquisition of HIV, potentially.

Labeling that would include a PrEP indication, along with risk mitigation strategies, could provide information for individuals and healthcare providers about the benefits and risks of PrEP, the importance of adherence, HIV testing, and safer sex practices, including condoms. But with the benefits, we must balance that with the risks. And what are the potential risks? The risk of development or acquisition of resistant HIV-1 variants; toxicity of long-term antiretroviral therapy; and the potential for behavioral compensation.

This afternoon, we'll be asking our advisory committee members questions related to risk/benefit, including the populations for which PrEP may be indicated. We'll ask about safety assessments, including frequency of HIV testing,

development of resistance, and monitoring for key toxicities, including renal and bone toxicities. We'll ask about risk mitigation strategies, postmarketing trials, and future clinical trial designs.

I'd like to end with a quote from U.S. Secretary of State Hillary Rodham Clinton in a speech delivered to NIH in November of 2011. And I quote: "Our efforts have helped set the stage for an historic opportunity, one that the world has today, to change the course of this pandemic and usher in an AIDS regeneration."

Thank you very much. And I also want to mention that Dr. Vega is sharing her birthday with us today, and we greatly appreciate that as well. Thank you.

DR. VEGA: Thank you.

DR. FEINBERG: Thank you.

We will now proceed with the guest speaker presentation, Dr. Susan Buchbinder, who is director of the HIV research section of the San Francisco Department of Health.

Guest Speaker Presentation –Susan Buchbinder

DR. BUCHBINDER: Thank you. I have been asked by the FDA to speak about the epidemiology of HIV infection in the United States, and to talk about what we know about risk and the potential for risk disinhibition.

So I've divided my talk into basically three sections. The first is to talk about who's most heavily impacted in the United States. The second is to look at what's driving the HIV epidemic in men who have sex with men and in heterosexuals. And the third is to talk about what we know about behavioral interventions and how they might be protective, as well as the possibility of risk compensation. And then I'm going to close with just a couple of remarks about the role of prevention strategies, given that we now have such an effective method of preventing transmission by treating an HIV-positive individual.

So these are the data which were first published in 2008, which were the first update of incidence data in essentially a decade, in which

new HIV infections were tracked in different risk groups. And what you can see is that for men who have sex with men, which is this sort of dark blue line, that the number of HIV infections really peaked in the mid-1980s.

Then through changes in social norms and increase in condom use, there was a really dramatic decline in HIV infections. But, as I'll get into later, there's been a steady increase in the rate of new HIV infections in men who have sex with men since the mid-1990s.

The group that is on my slide shown in pink are injection drug users, which represent another actual great breakthrough in prevention, in that the HIV infection rate in the mid-'80s to early '90s remained relatively level. But then there was a relatively dramatic decline in the rate of new infections, and that's remained very low, in part due to the provision of clean syringe and injection equipment.

The heterosexual epidemic in the United States lagged a little bit behind the other two

epidemics, so it peaked, really, in the late 1980s. And unfortunately, it's remained at a pretty steady level since that period of time.

So what I'm going to do next is to review, based on risk category, based on race/ethnicity, and based on age, the epidemic in the United States to highlight who's most heavily impacted. There was a slide shown just before this that looked at the proportion of new infections attributable to each of the risk groups. This is actually a slide showing the number of diagnoses.

You can see that men who have sex with men account for the vast majority of new infections, and that it's also the only group in whom new infections are continuing to increase. And this is an absolute number of infections. This is not a rate per 100,000 MSM population, which you can imagine is quite high, and quite a bit higher than any other population in the United States.

If you then combine risk group with race/ethnicity, what you can see is that the three most heavily impacted groups in terms of number of new

HIV infections are men who have sex with men, white, black, and Hispanic men who have sex with men. And I'm going to get in a moment into how this relates to the size of the population and the case rate. Then the second group that's most heavily impacted are black heterosexual women and men.

So if we take into account the population sizes, what you see is that men are shown on the top in blue and women on the bottom in pink. This is not my graphic.

(Laughter.)

DR. BUCHBINDER: And black men and women have much higher rates per 100,000 population than Hispanics, and they have a much higher rate of new infections than white individuals in a rate-per-100,000 population. So there clearly are substantial racial and ethnic disparities in the rates of new HIV infection in the United States.

If we then look at age, and these are rates of new HIV infections by age group among men who have sex with men, what you can see is that the two

groups in which new HIV infections continue to rise, actually somewhat steeply, are the 13- to 24-year age group and the 25- to 34-year age group.

Nonetheless, the 35- to 44- and 45- to 54-year age groups still have substantial rates of new HIV infections. And so this is really an epidemic that is striking men who have sex with men at all ages, but the concern is that the rates are increasing in younger men who have sex with men.

If we then look at the subgroup of men who have sex with men in the 13- to 24-year age group, you can see that the group that is overwhelmingly most heavily impacted are black, young, men who have sex with men. And again, the group of Latino men who have sex with men, although the numbers are similar to the white population, because it's a much smaller population in the United States than the white population, the Latino men who have sex with men are also very disproportionately affected.

If we look at women and the risk factors for infection in women, you can see that in black or African American women, in Latina women, and in

white women, the overwhelming majority of infections is caused by heterosexual contact. And even among the injection drug users, they may be exposed through sexual exposure rather than injection drugs.

Again, we see the same racial and ethnic disparities in women, with higher rates per 100,000 population in black women compared to Latina women. And that's higher yet again compared to white women. But you also see that there are these regional variations, and I'm going to get into this in a little bit as well, with highest rates of new HIV infection in the Northeast and in the South.

So now I want to talk about what's driving the epidemic in these two populations. These are data from the EXPLORE study, which was a study of over 4,000 men who have sex with men in six U.S. cities. It took place about a decade ago. But we've had a number of studies before, as well as a number of studies after, that show pretty much the same factors driving the epidemic in men who have sex with men. And what I'm going to be focusing on

is the population-attributable risk, although I will mention the adjusted odds ratios.

What you can see is that the single largest population-attributable risk comes from having multiple partners. Having unprotected receptive anal sex, however, also is clearly driving the infection.

That's true not just for known HIV-positive partners, who have a population-attributable risk of 18.2 and obviously the highest odds ratio, adjusted odds ratio, but also particularly among partners who are having unprotected receptive anal sex with partners of unknown serostatus as well as HIV-negative serostatus because, unfortunately, some of the partners who are believed to be negative may not be negative and may be unaware of their HIV infection. And then the third substantial factor that's driving HIV infection in men who have sex with men is the use of substances.

So what's driving infection rates in heterosexuals? And these comments that I'm making are specifically around heterosexuals, but they

also apply to men who have sex with men because we see these really substantial racial and ethnic disparities.

What we know, actually, is more limited in the heterosexual epidemic than in the MSM epidemic because there have been a number of longitudinal studies of infection in high-risk women, and although pregnancy rates and rates of sexually transmitted infections may be high among populations, HIV infection rates may still be low. That's really dependent upon the prevalence of HIV in the partners. Women are often unaware of their partners' risk factors or their HIV serostatus.

So there are number of factors that are driving the epidemic; but really predominately, in the CDC's national surveillance survey in 2006 and '07 for heterosexuals, the primary independent risk factors really were poverty, having less than a high school education, and unemployment.

These factors, particularly poverty and lack of access to healthcare, as well as sometimes the need to exchange sex for drugs or money, leads to

these differences in mixing patterns. And there's also a higher ratio of men -- I'm sorry, a lower ratio of men to women, particularly in the black population. That may or may not lead to increased rates of concurrency. But clearly, there are differences in HIV infection status within sexual networks.

So both for men who have sex with men and for heterosexuals, the levels of risk are no higher, and in fact in many cases are actually lower, than, for instance, in the white population. But because the prevalence of HIV infection is so much greater within sexual networks, the rates of HIV infection are higher.

So it really isn't about individual behavior. It's really about structural factors that's driving the epidemic, particularly in the heterosexual population, but also likely in the men who have sex with men population.

The question always comes up, well, we have condoms. So why aren't condoms completely effective? And there are any number of reasons,

but I'm just listing four here.

The first is that condoms don't always work. There is breakage and slippage of condoms. It's reported to be between 1 and 2 percent per act for vaginal sex, and substantially higher for anal sex when substances are in use, when people are inexperienced with condom use, and when either lubricants aren't used or oil-based lubricants are used. So condoms are not perfect, and they're not perfectly protectable, though practice does make perfect. It does help.

There are a substantial proportion of men who report sexual dysfunction when they use condoms. So that also is a factor that inhibits their use. Main partners are more likely to report that they're not using condoms within their partnership, in part because of issues of intimacy and trust and what that's communicating if there's a request that condoms be used. And then there are a substantial proportion of serodiscordant couples in the United States who describe pregnancy, in which case condoms could not be used.

So let's talk a little bit about what we know about behavioral interventions and risk compensation. We say that there's been an evolution in our thinking about counseling and its impact on HIV infection.

So Project RESPECT in the early 1990s became the standard of care of practice for counseling, in which, rather than four counseling sessions, two counseling sessions were equally protective in both the risk of sexually transmitted infections -- not HIV, but sexually transmitted infections -- as well as risk practices. So the standard became a two-session intervention.

With RESPECT II that took place in the late '90s, there was a comparison of rapid versus standard testing, and with the rapid testing, then just one session of counseling. And in this situation, rapid testing was a benefit over standard testing because more people were getting their test results, with no increased risk of sexually transmitted diseases or behavior, and no benefit from an additional booster counseling

session given to individuals with a single episode of counseling. And then just published this year are data from a study in injection drug users, showing that rapid testing without counseling resulted in no increased risk compared with rapid testing with counseling.

So I think gradually -- and the CDC has moved away from this recommendation that everybody needs extensive post-test counseling to really focusing our efforts on post-test counseling for known HIV-infected individuals and linking them into care rather than counseling for HIV-negatives because there's no evidence that finding out your negative test results actually reduces HIV risk practices. Finding out your positive test results, on the other hand, does. And so the focus is really on counseling and care for HIV-infected individuals.

This is the EXPLORE study in men who have sex with men, in which what was called the Cadillac version of behavioral interventions was given to men who have sex with men, a 10-session

intervention that was client-centered. And there was no reduction in the risk of HIV infection in this study.

So the challenge is that we have a number of behavioral interventions, but none of them have an HIV incidence endpoint. Most of them show modest reductions in self-reported behavior. But we have to remember that EXPLORE also showed a modest reduction in self-reported behavior, with no apparent reduction in incidence, which may either be because the level of reduction in risk was not great enough to drive a reduction in incidence, or it may be about social desirability and over-reporting condom use or under-reporting risk. And then most of the behavioral interventions have very short follow-up, and they often have difficulty with retention.

So the individual-level interventions, behavioral interventions for HIV-negatives, are not offering us a lot more in the way of prevention -- that's my personal opinion -- but, on the other hand, couples-based interventions can

increase rates of HIV testing as well as medication adherence for the HIV-positive partner. So I think, again, there's been a shift towards where we should be focusing our efforts.

Now, this question about risk compensation comes up repeatedly. And what we know is that in the setting of trials -- vaccine trials, PrEP trials, whatever kind of prevention trials there are -- there's generally a decline in risk practices when people get into these studies. And presumably, in part it's getting into care as well as other cohort effects.

Lynn Paxton's going to be presenting data on the CDC U.S. MSM PrEP study, in which we randomized individuals to take either a pill immediately or wait nine months before taking a pill, to compare whether pill-takers had increased risk compared to the delayed group. And there was no increase in risk. And she'll show you those data in more detail. However, obviously that was done in placebo-controlled trial, and it was done before we knew what the efficacy was.

So I think the bottom line is we don't really know what's going to be happening with risk compensation in a real world setting. What we know from male circumcision trials is that it appears that there's not a generalized increase in HIV infection rates within populations, although there may be some subgroups of men who are increasing their risk. And so I think that's something that we might expect.

So I'm going to be borrowing a slide from Jared Baeten that he presented at CROI, in which if you compare primary prevention of HIV infection in iPrEx -- where you have a life-threatening illness, HIV infection, that is in part behaviorally driven -- with a 4 percent incidence per year in the placebo arm and a statistically significant but not completely efficacious intervention -- and you compare that to the use of statins to treat cholesterol, again with a life-threatening illness, for something that's driven in part by lifestyle, with a lower attack rate in the placebo arm and a lower relative risk reduction -- there really

hasn't been a lot of concern about risk compensation. We're not asking people, are people who are on statins going to be eating more ice cream?

In fact, when I was looking for articles on risk compensation, there are many articles on risk compensation in the HIV field, and almost none in the statin field. And in fact, I found an article in the American Journal of Cardiology that was suggesting that, actually, one statin pill offsets a quarter pounder with cheese and a small milkshake, and was recommending, actually, that maybe what we really need to do is dispense statins along with the condiments at fast food restaurants.

(Laughter.)

DR. BUCHBINDER: So there's a whole different approach to risk compensation in other fields.

These are data from Ume Abbas, and it's a model looking at how effectiveness influences the population effect of risk compensation. And what I just wanted to point out is this is a somewhat

complex slide with the sort of cooler colors, from green over to blue, demonstrating a net reduction in HIV incidence rates in a population, and the yellow to the red showing a net increase in HIV infection rates.

If you look at a highly efficacious intervention, vaccine or PrEP, what you see is that you can tolerate fairly large degrees of increases in risk practices without suffering any reduction in population-level effectiveness; so that what we really do need to focus on is getting interventions that will get us to higher levels of effectiveness.

So I'm going to end by talking a little bit about treatment versus prevention because we now have the HPTN 052 study that suggests that you can get a 96 percent reduction in HIV transmission from an infected partner if they're adequately treated. But it's the "if they're adequately treated" that's the catch.

So even in the United States, it's estimated that in going from HIV infection to diagnosis to getting linked to care, retained in care, on

antiretrovirals, and then with a suppressed viral load, that only 28 percent of the HIV-infected population has a fully suppressed viral load in the United States. And that's despite many efforts to improve that.

Then Gardner published a study last year that suggested that if you could be wildly successful in any one of these areas -- 90 percent of the infecteds are diagnosed, or 90 percent of those diagnosed are engaged in care, and so on and so forth, and the yellow bars show the proportion with undetectable viral loads -- it's only if you achieve 90 percent success in each of those categories that you get a 66 percent of the HIV-infected population with an undetectable viral load.

So we need to strive for this, but it's not going to be the only answer. And so my answer to the question about treatment or prevention is that it really has to be treatment and prevention, that the only way that we're going to end the epidemic is through a concerted combination approach.

So my conclusions are that in the United States, populations at greatest risk are men who have sex with men, particularly young men of color, and low socioeconomic status heterosexuals, especially black women.

Risk is driven by structural factors as well as individual factors. So we have to remember that it's not really just all about behavior, it's really about environments, and people often don't have control over their environments.

Risk compensation may occur in subsets of individuals, and we don't yet know what the impact of that will be. Individual-level behavioral interventions, however, are inadequate, and what we need are new treatments and prevention strategies to have a major impact on the U.S. epidemic.

Thank you.

DR. FEINBERG: Thank you very much, Dr. Buchbinder.

Our next speaker will be the guest from the CDC, Dr. Lynn Paxton, who's a captain in the United States Public Health Service, a medical

epidemiologist in the epidemiology branch. And she's going to present to us the CDC PrEP studies. And then we'll entertain clarifying questions from the committee for both speakers when she's finished.

CDC Presentation – Lynn Paxton

DR. PAXTON: Thank you. I'd like to thank the FDA for allowing me to present on behalf of the Centers for Disease Control.

I will be presenting, in this study, results from our CDC PrEP trials. I have highlighted the fact in the first bullet that we are conducting a trial of tenofovir alone among injection drug users in Bangkok. However, that study began in 2005. We have reached our endpoints, and we expect to release the results in the third quarter of 2012. So I will not be presenting the actual results of this trial today.

I will also be presenting the monkey studies, the macaque studies, that contributed greatly to the human clinical studies, as well as the U.S. MSM safety study, which is the one

referred to as 4323 in your materials, and the Botswana TDF2 study.

So to start with the macaque studies, this slide basically shows that in what we call our low-dose study, in which macaques are exposed weekly to low-dose -- well, actually, this dose is actually the human equivalent of approximately five times what you might see in primary infection. You'll see that in the control group, most macaques were infected by 14 weeks.

As we increased the potency of the regimen given to them, going from oral tenofovir through subcutaneous FTC, to oral FTC/TDF, and up to the highest potency regimen of subcutaneous FTC, high-dose tenofovir, we found increasing efficacy.

We also found that this held true for intermittent use of oral Truvada among the macaques. And so as compared to the untreated controls, we found that giving various regimens of oral Truvada, both pre- and post-exposure, showed efficacy, even including giving the drug as early as seven days prior to exposure. But what is not

shown on this slide, which is very important, is the importance of this post-exposure dose. In studies that I'm not showing here in which we did not give the post-exposure dose, it was ineffective.

We have found also that this retains efficacy when used in the model in which the SHIV dose given was FTC-resistant. And so we found that among those macaques that were treated 3 days before and 2 hours after, that we were still able to prevent HIV infection with this FTC-resistant mutant. Presumably that is because the presence of the M184V mutation does provide about approximately threefold increased sensitivity to tenofovir.

So the summary of these studies show that we think that this data is actually consistent with the iPrEx results. We did see a clear dose-response relationship observed in that higher -- we saw a higher efficacy with the two-drug regimen than with tenofovir alone, which is one of the reasons why we decided to switch some of our studies to looking at Truvada. We found that

intermittent Truvada was also effective, and that the efficacy was maintained against FTC-resistant virus.

So I'm going to now present the 4323 study. This was a randomized, double-blinded, placebo-controlled safety trial which took place in three sites, in Atlanta, in San Francisco, and in Boston. We had 400 HIV-uninfected MSM who were randomized to receive either tenofovir at 300 milligrams per day or placebo.

They had visits every 3 months in which they underwent HIV testing. They were assessed for adverse events and the laboratory safety parameters, asked about their adherence, and we collected sexual and sociobehavioral data, and they received extensive risk reduction counseling.

There was a bone mineral density study that was done among the San Francisco participants. I will not be presenting that data, as Dr. Miele will be presenting it in his presentation later today.

This is the study design, which shows what Dr. Buchbinder highlighted, in that half of the

cohort was assigned to receive no pill for the first nine months, and they then received either tenofovir or placebo. This was to judge the behavioral effects of receiving a pill versus not receiving a pill.

These are the baseline participant characteristics, basically showing the groups were comparable. This was a mostly white population and also highly educated, with about almost 90 percent having some college education.

I'm just highlighting the fact that the one adverse effect that had a significant P score was that of back pain, which was higher in the group receiving tenofovir. The others were all comparable between the two groups.

Now, these next three slides are going to show the reported number of behavioral characteristics. And this one shows that the mean number of sex partners did not differ between the immediate and delayed arms, and also, as Dr. Buchbinder highlighted, became lower over the course of the study.

Similarly, we found no difference in the reported unprotected anal sex by the immediate versus delayed arms. And that also seemed to remain steady over the course of the study. And this is the mean number of USA episodes, again, by intermediate and delayed arms.

So now I'm going to move on to the TDF2 study, which took place in Botswana. This again was a double-blinded, placebo-controlled trial of Truvada, TDF/FTC. And our study population was actually exactly 1,200 male and female Botswana citizens between the ages of 18 and 39.

They were seen every month and tested for HIV infection, again, monitored for illness and side effects. The adherence was a success by multiple measures, including self-report, pill count, and drug levels, which occurred among -- we have a case control study at the end of the study; we have not yet assessed the entire group using the drug levels.

This is just to show that the two groups, the after-drug arm and the placebo group, were

comparable. We had approximately 45 percent of our population were women.

Now, this slide shows what we refer to as our intention-to-treat analysis, which includes all persons who were randomized to receive either active drug or placebo. We had a total of 36 seroconverters in the trial. However, on retrospect of testing, we found that three of them were infected upon enrollment, so they have been removed from this analysis, and this is the remaining 33. There were 9 people who were HIV-infected in the Truvada group, and 24 in the placebo group, which gave an overall protective efficacy of 62.6 percent.

When we restricted analysis to those participants who seroconverted within 30 days of their last dispensation of medication, we found that there were 4 people in the Truvada group and 19 in the placebo group, which gave an overall protective efficacy of 77.9 percent of this group, which we refer to as the participants who were on study at the time that they seroconverted.

Now, this is our breakdown of infections by gender. Again, because of our small numbers, some of these do not reach statistical significance. But using our modified intention-to-treat analysis, we found efficacy for both females and males, although it was not statistically significant for females. When we restricted it to the 23 seroconverters who seroconverted while on study, we found efficacy in both females and males.

This is from the case control study that I just mentioned, in which we took all the seroconverters who had been assigned to Truvada and compared them with matched controls. And we found that there was a relationship between having detectable Truvada or FTC in the blood and protection.

Our safety parameters show that this was remarkably safe in this group. There were only three adverse events that were statistically significantly more present in the Truvada group, and that was dizziness, nausea, and vomiting.

As you'll see from the next three slides,

while there was this difference in reporting between the two groups, in both groups it decreased over the longer that someone was on drug and became comparable between the two groups over time. So that was for nausea. This is for dizziness, and this is for vomiting.

We did have two cases of drug resistance in this group. One participant was assigned to the Truvada arm. This person came into the study with unrecognized, acute, wild-type infection and was started on Truvada. This person did develop mutations at high levels; K65R, the M184V, and also the A62V mutation were found.

Just as a clinical follow-up, this person was started on a regimen that did not contain either of these drugs, and is doing well on an alternate regimen with an undetectable viral load. We had one participant in the placebo group who came in with a K65R mutation at very low levels.

This is the results from our bone mineral density study. What we did is we did a sub-study among participants at our Gaborone site, and we had

221 participants in the sub-study; 109 of them were on Truvada, 112 on placebo. About 107 were males and 114 were females.

Even at baseline, we had a significant number of people who presented with Z-scores that were more than 2 standard deviations below the mean, 2.63 percent of our women and 11.3 percent of the men.

So this is looking at the follow-up data for both the men and the women. And I combined them in this slide because we did not find any differences between men and women. So it's combined here.

So we found for the forearm, that the net effect of Truvada on BMD was a decrease of negative .88 percent. For the DEXA scan of the spine, again there was an effect, and that was about negative 1.66 percent, and at the hip it was negative 1.53 percent.

So the conclusions from these studies is that both tenofovir and Truvada were safe for both males and females. Truvada was effective in preventing HIV infection among both males and

females in our TDF2 study, and both tenofovir -- and I have not presented that data, but Dr. Miele will -- and Truvada were associated with small but statistically significant decreases in bone mineral density.

These decreases in bone mineral density were not associated with any increased risk of fracture. And there was no evidence for behavioral disinhibition in either trial.

I think I'm actually coming before time on this. So I hope you're grateful to me for giving you an extra 7 minutes.

(Laughter.)

Clarifying Questions from the Committee

DR. FEINBERG: Thank you very much, Dr. Paxton.

So let me open this up to the committee. Do you have clarifying questions for either Dr. Buchbinder or Dr. Paxton?

DR. PADIAN: I have a question for --

DR. FEINBERG: Excuse me. Please remember to state your name before you speak.

DR. PADIAN: Oh, okay. Nancy Padian.

Lynn, in the macaque studies, did any of the animals have only post-exposure and not pre?

DR. PAXTON: Yes. I believe that they did, and I believe that it was -- I'm sorry. I don't want to make up data. I'm trying to remember. I do believe that there were a few -- there was a study in which they did do only post-exposure prophylaxis, and there was some efficacy, but not as much as what the pre-exposure does. So we found that both were necessary for protection.

DR. WOOD: Dr. Lauren Wood. If you go back to your slide on TDF2 infection by gender, when you go from 33 down to the 23, it was nonstatistically significant in women but it was in men. But then when you go down to 23 seroconverters, it's more statistically significant in women, but it looks like it's trending toward being less statistically significant in men.

Could you comment on that?

DR. PAXTON: Well, I think that this all comes down to the fact that we had such small

numbers. If you see, we only had 23 people who were actually on study at the time that they seroconverted.

So we feel that, given the trends that we see here, that most likely if we'd had more people in the study, if it had run longer, that we probably would have found that both of these would have been statistically significant.

DR. FEINBERG: Dr. Strader?

DR. STRADER: Doris Strader. I have two questions for you, one for Dr. Buchbinder. They should be pretty brief.

First, in your baseline characteristics slide, I'm still confused about how it's possible to have 45 percent female patients in a heterosexual couples group. Should they be even?

DR. PAXTON: We were not a discordant -- people were not enrolled as a couple. They were enrolled as individuals.

DR. STRADER: Hmm. Okay. So one person as an individual may or may not have HIV, and their partner, whoever that person was --

DR. PAXTON: No. In order to enter this study, you had to be HIV-negative. You did not have to enter with your partner.

DR. STRADER: I see. All right. And were the patients in this study tested for renal toxicity? You mentioned bone marrow --

DR. PAXTON: Yes, they were. Everyone was tested. They had creatinine, phosphorus, and they had a number of laboratory parameters that were tested. I did not present them on this slide, although I think I do have them as a backup slide. But basically, we did not see any differences in -- oh, I'm sorry. I guess it was in here as a backup.

Anyway, we did not see any differences between the placebo and the -- I'm sorry about the slides. Excuse me. I don't even have the excuse. My car didn't even blow a tire today, so --

(Laughter.)

DR. STRADER: And for Dr. Buchbinder, could you explain the mixing patterns a little bit more for me to understand what you mean?

DR. BUCHBINDER: Yes. So this is a very complex field that I would not in any way claim to be an expert in. But the question is, really, how is it that in some groups, the same levels of risk that are reported can lead to very high levels of infection, and in others lower levels of infection.

Dr. Millett at the CDC has actually published extensively on this issue, that, for instance, young black men who have sex with men have substantially lower rates of reported risk but also higher rates of HIV infection. And we believe that that probably has to do with sexual networks, so that if there is a lot of HIV infection within a particular sexual network and individuals within that network are exposed, that they're much more likely to become infected than individuals in another network who may even have higher levels of unprotected sex, but if they're not being exposed to HIV, then they won't become infected.

So in our studies of women, we've had a great deal of difficulty in finding cohorts of women with high seroincidence rates over time in

which to test, for instance, vaccines because these women are clearly having a lot of unprotected sex. Rates of pregnancy are very high. Rates of sexually transmitted infections are very high. But if there isn't HIV infection in their male partners, then they're not going to become HIV infected, which is obviously a good thing. But that makes it very difficult to identify which women are at very high risk. And that's why it really does appear to be more a socioeconomic factor and a factor of what's happening within sexual networks than necessarily about individual risk.

DR. FEINBERG: Dr. Ellenberg?

DR. ELLENBERG: I have a question for each speaker.

Dr. Paxton, with regard to the fractures, it looked like you had about 24 -- you showed follow-up of 24 months, so that's not a hugely long period of time. How many fractures were actually observed in this study, and have you done any modeling to project what a longer-term effect might

be for people taking this medication for a long time, and what that would mean for fractures over a period of 5, 6, 8, 10 years?

DR. PAXTON: Yes. I'm just looking this up right now. We did have -- I'm trying to see if I can find this. In the TDF2 bone marrow density study, we had two participants, one in each arm, who sustained traumatic fractures. None had atraumatic fractures. I believe that in the study as a whole, we had 11 fractures, again equally distributed between the two groups, all related to trauma.

I might have to call on Susan to help remind me about the number of fractures in the U.S. study, the 4323.

DR. BUCHBINDER: That was also equal between the two arms, and was not related to bone mineral density. And they were all traumatic fractures.

DR. ELLENBERG: Can I ask another question? I'd like to ask Dr. Buchbinder about the risk compensation. You talked a little bit about it. That was an interesting comparison with statins; of

course, the difference between somebody taking a statin that directly affects themselves versus somebody preventing an infectious disease actually has effects for others, so I'm not sure the analogy holds up completely.

But I sort of took from what you said about this that you didn't really think risk compensation was an issue that we needed to worry about very much.

Is that your message?

DR. BUCHBINDER: No. That's not really what I'm saying. I guess what I'm saying is that I think we don't know. I think there are three levels of evidence that we might have. The first is, what happens in these trials? And what we can say is that when individuals enter trials, prevention trials, that there is a reduction in risk generally in both arms of the trial.

The second tier is that when we actually try to introduce a randomized component in trials, about taking a pill early versus late, that we didn't see any evidence of risk compensation. Now,

again, both of these are in the setting of a placebo-controlled trial, and also, a substantial amount of risk reduction counseling that happens in the trials.

So the third level of evidence really is going to be, once people know what the level of efficacy is and they know that they're getting the active pill, will risk change over time? And I believe that Dr. Grant is going to be talking about the open label extension of the iPrEx study, in which we are trying to ask that question.

I will say that -- I'm not saying that we don't need any counseling in the context of pre-exposure prophylaxis being dispensed, that it may be that -- I guess my point about the cardiovascular community was -- the idea there was that they were saying, what we need to do is we know behavior is not enough. In fact, in some articles they said, we know behavior isn't enough. And so what we know is that we need to layer on top of that -- without abandoning our attempts to try to help people to have healthier diets and

exercise, we need to layer on top of that a biomedical prevention intervention.

So I'm just saying that if we have high levels of effectiveness, then risk compensation may be less concerning, and that what we need to try to do is figure out how we -- all of the cardiovascular studies are talking about how do you combine counseling with statins, not how do you choose one over the other.

DR. FEINBERG: Are there any other questions from the panel?

DR. DASKALAKIS: One quick one. Demetre Daskalakis from NYU. Could you actually comment on any behavioral data that you have on the two CDC studies, the MEMS safety and the TDF2?

DR. PAXTON: Yes. Actually, we found that in the TDF2 study, most of our participants actually reported having only like one steady partner or two steady partners. Most of the participants reported that they used condoms. It was usually about 90 percent.

I didn't mention it, but our adherence

numbers in that study, in the TDF2 study, were by pill count and reported. And our adherence by self-report was 92 percent, and our adherence by pill count was 84 percent. The related question is, do we believe all that? And the answer would be no, but that's what we had that was reported to us.

What we found also was that over the course of the study, in fact as Susan has pointed out numerous times, that actually reported risk behavior tended to decline, to stay the same or to decline. And we found similar things in the U.S. study 4323, in that adherence by pill count was 92 percent. And in that study we also used MEMS caps and median adherence, and that study was like 77 percent.

DR. FEINBERG: Dr. Estrella?

DR. ESTRELLA: Hi. I had a question for Dr. Paxton, actually. I just wanted to ask you if you could please describe the baseline characteristics of the participants in terms of risk factors, traditional risk factors for kidney

disease, diabetes, hypertension, and if there was any cutoff for estimated GFR or kidney function to enter the trial. Thanks.

DR. PAXTON: You're talking for both trials or for the --

DR. ESTRELLA: The PrEP trial.

DR. PAXTON: I'm sorry, what?

DR. ESTRELLA: For the PrEP trial, the CDC PrEP trial.

DR. PAXTON: The U.S. trial?

DR. ESTRELLA: Yes.

DR. PAXTON: Susan, help me out on this one. We did have criteria under which people had to enter into the trial. They could not have diagnosed renal deficiency or the like. But in terms of hypertension and the other things, I do not believe -- I'm not intimately familiar with what the criteria was. I know that people had to be healthy to enter into the trial.

DR. BUCHBINDER: Right. And so we did rule out people who had baseline reductions in GFR. And we also had pretty strict criteria for taking

people off of study drug; we followed their creatinines closely. But we did not see evidence of renal toxicity.

DR. PAXTON: And so similarly -- I'm a little bit more familiar with the TDF2 study in Botswana -- we had very similar criteria. They had to have normal creatinine clearance to enter into the trial, and they had to maintain that over the course of the trial. We did not have anyone who had to come off, I believe, because of any changes in creatinine.

DR. FEINBERG: Dr. Giordano?

DR. GIORDANO: Thank you. This is a risk compensation question. On the study with deferred versus immediate PrEP, the self-reported risk was no different in the two arms, as I understand it, after therapy started.

Was there difference in STI diagnoses in the deferred versus the immediate arm?

DR. PAXTON: No.

DR. BUCHBINDER: But the rates were fairly low.

DR. PAXTON: Yes. And that's similar for the Botswana trial. We didn't have any differences, and they were very, very low.

DR. FEINBERG: Dr. Cheever?

DR. CHEEVER: So my first question may not be able to be answered if the rates were very low, which was, looking at the efficacy if a patient had a concurrent STI, the efficacy of PrEP.

DR. BUCHBINDER: If a patient had concurrent STI? I don't know that you can --

DR. PAXTON: Yes. We can't say anything about that. We had such low levels of STI, even at baseline, and actually that even fell over the course of the study, I think probably -- almost certainly -- due to the enormous amounts of risk reduction counseling that people received and the condoms and the like.

DR. CHEEVER: My second question was around hepatitis B, if, one, that was an exclusion in these studies, have chronic hepatitis B; and two, what is the vaccine coverage rate for young MSM for hepatitis B vaccine at this time?

DR. PAXTON: Well, I can just say for both studies it was an exclusion criteria. I think, Susan, you might be able to better answer the second question.

DR. BUCHBINDER: It's not what it should be. I can't give you an exact number, but it is something that we try to offer participants. And it may be that Bob Grant has data on the proportion who came in to iPrEx initially unvaccinated, but I don't have the exact number. But I could get that for you.

DR. FEINBERG: Mr. Raymond?

MR. RAYMOND: Thank you. I'm wondering, for the CDC study, if you had behavioral data on substance use amongst the study participants and whether that was affected during the course of the study at all.

DR. PAXTON: Well, in Botswana, we didn't have any -- I think we had one person who reported substance use. I mean, if you're not including alcohol --

MR. RAYMOND: Including alcohol.

DR. PAXTON: No. Well, then, that markedly changes. Then we had significant -- when I say significant, we had about maybe 40 percent of the group reporting that they had used alcohol in the past month or so. However, this was not -- we don't have an estimate of abuse of alcohol. This was just simply asking have you had one or more drinks in the past month? We did ask about alcohol use in conjunction with sex, in terms of had they used alcohol before sex.

Susan, I'm going to again defer to you. She's much more familiar about the -- there was a much higher degree of substance use in the U.S. trial.

DR. BUCHBINDER: And it differed by city, so that the kinds of substances and the rate of substance use were different in San Francisco, Atlanta, and Boston. And in general, substance use also goes down over time.

I don't believe -- and I'll see if I can see -- there we go. I believe that we looked at changes in substance use between the immediate and

delayed. Did we do that?

UNIDENTIFIED SPEAKER: (Inaudible – off mic.)

DR. BUCHBINDER: With risk, yes. So there certainly is substantial substance use in the men who have sex with men participants who are enrolled, and generally, that goes down somewhat over time. But it also depends on what the substance is. We do try to link people into treatment programs, and they do get counseling around substance use. And it is, unfortunately, also associated with HIV infection.

DR. FEINBERG: Let me just remind the audience that no one can speak without the chair's acknowledgment.

DR. BUCHBINDER: Oh, sorry.

DR. FEINBERG: So that if a presenter -- if you want to turn to somebody in the audience that has information, you have to ask about that first.

DR. BUCHBINDER: Thank you. I will do that.

DR. FEINBERG: Are there any other clarifying questions from the committee?

Dr. Corbett?

DR. CORBETT: I wanted to know if I could ask about the tenofovir and FTC levels from the TDF2, and if these were extracellular or intracellular concentrations.

DR. PAXTON: What I have presented here is what we had available about a few months ago, and that was simply the plasma levels in this case control study. We are getting the PBMC levels done for the TDF2, but I did not present that.

DR. FEINBERG: Thank you both very much. Then if there are no other questions, we'll move on to the sponsor presentation.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. So to ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee

presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the outcome of this meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

So we will now move on to the overview of Truvada from Dr. Andrew Cheng, senior vice president, HIV therapeutics and development operations, Gilead Sciences.

Sponsor Presentation – Andrew Cheng

DR. CHENG: Good morning. My name is Andrew Cheng. I'm the leader of the HIV therapeutics and development operations group at Gilead Sciences. On behalf of Gilead Sciences, we thank the

committee, the FDA, our colleagues from the NIH and the CDC, the community of HIV healthcare providers, and the community of patients for this opportunity to present our data supporting the use of Truvada for pre-exposure prophylaxis indication for HIV-1 infection.

Over the next 90 minutes, the committee will hear five presentations. Following an overview of the Truvada program in the treatment of HIV infection, Dr. Robert Grant from the Gladstone Institute and the University of California at San Francisco will present findings from the iPrEx study demonstrating the safety and efficacy of Truvada for PrEP indication in MSMs.

Drs. Connie Celum and Jared Baeten from University of Washington will then present findings from the Partners PrEP study, demonstrating the safety and efficacy of Truvada for PrEP indication in serodiscordant partners. The 90-minute presentation will conclude with a presentation on resistance and closing comments by Dr. John Mellors from the University of Pittsburgh. Let's begin

with a review of Truvada.

Stemming the tide of HIV infection requires a multifaceted approach capitalizing on a variety of prevention opportunities available in our HIV prevention toolbox. PrEP is intended to be an addition to the HIV prevention toolbox, not to replace any of the existing tools.

Gilead Sciences proposes an indication for Truvada's pre-exposure prophylaxis. Truvada is indicated for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults.

The following points must be considered when prescribing Truvada for pre-exposure prophylaxis; that is:

That the indication is based on studies in MSM at high risk for HIV-1 infection and heterosexual serodiscordant couples.

Truvada should only be used as part of a comprehensive prevention study because Truvada is not always effective at preventing the acquisition of HIV-1.

All uninfected individuals should be counseled to strictly adhere to their Truvada dosing schedule because the effectiveness of Truvada in reducing the risk of acquiring HIV-1 is strongly correlated with adherence and detectable drug levels.

Uninfected individuals taking Truvada for PrEP should have a documented negative test prior to initiating and routinely taking Truvada for PrEP.

Truvada for PrEP should not be initiated if symptoms of acute HIV infection are present.

The regulatory history of Truvada was mentioned, touched upon, by Dr. Birnkrant this morning. Truvada was approved in 2004, with the individual components, tenofovir DF and emtricitabine, being approved in 2001 and 2003 respectively. Subsequent to the approval of Truvada, it was incorporated into two single-tablet regimens, Atripla in 2006 as well as Complera in 2011. Tenofovir was also approved for the treatment of hepatitis B in 2008.

All told, our cumulative worldwide safety database for the components of Truvada, emtricitabine and tenofovir DF, are roughly 8.9 million patient-years for the components of tenofovir DF, and for emtricitabine, roughly 4 million patient-years. Despite this extensive utilization, resistance rates over the last 10 years have continued to decline.

These are data from a monogram biosciences database looking at the incidence of K65R and M184V incidence. These are the signature mutations for tenofovir DF and emtricitabine, respectively.

Over the period on the graph, you can see that, roughly, there's a 48 percent reduction in M184V and a similar reduction in K65R. This is despite increasing usage of Truvada in the treatment of HIV. As noted previously, Truvada is the preferred nucleoside backbone for the treatment of HIV.

We will address several aspects of the safety data that are the primary events associated with Truvada, that is, renal impairment and changes

in bone mineral density. Let's begin with the controlled clinical trial data.

These are data from a 3-year randomized study comparing Truvada plus efavirenz versus Combivir plus efavirenz in the treatment of HIV and HIV-uninfected individuals. The entry criteria for renal parameters in this study was 50 milliliters per minute.

Over the 3-year period, both arms had a small decline in estimated glomerular filtration rate. The baseline was 121 milliliters per minute in both arms, and you can see that at the end of the 3-year period, in red, the Combivir arm had 118 milliliters per minute, and in comparison, the Truvada arm with efavirenz had 115 milliliters per minute. This difference was not statistically significant.

In the iPrEx and Partners PrEP studies, the mild to moderate serum creatinine elevations with Truvada occurred in roughly 2 to 2 and a half percent of patients, with approximately 0.1 percent of permanent renal discontinuations.

We can look at the renal adverse event rates in HIV controlled clinical trials on the next few slides. When one looks at the adverse events in Truvada-containing trials, whether with a non-nucleoside reverse transcriptase inhibitor or with protease inhibitors boosted by ritonavir, we can see that the event rates for renal adverse events leading to discontinuation, serious renal adverse events, or proximal tubulopathy, range from zero to one-half percent with non-nucleoside reverse transcriptase inhibitors as the third agent, compared to approximately zero to 1.4 percent with protease inhibitors.

We've also looked at serum creatinine elevations in many of the trials. You'll note that the denominator has changed because these are data from publicly available sources, not all of whom have reported serum creatinine data.

When one looks at -- excuse me. It's also notable that the grading scales in some of these trials are different, that is that what is defined as grade 1 may be different from trial to trial.

But the rates of graded elevations from grade 1 range from zero to roughly 6 and a half percent in both trials with non-nucleosides and protease inhibitors; and for higher grade elevations, they range from zero to roughly 1 percent in each of the reported trials.

With graded proteinuria, again acknowledging that all trials have publicly reported this, the rate of proteinuria ranges from 4 to roughly 27 percent with non-nucs for grade 1, and for grade 2 events, roughly 1 to 5 percent.

Turning to bone, we also have controlled clinical data on bone mineral density in the tenofovir registration study, study 903. As a reminder, this study was a 600-patient randomized, double-blind, placebo-controlled study looking at changes in bone mineral density over a 3-year period.

We see significant decreases between the tenofovir and d4T arm from baseline. However, it is notable that the decrease in tenofovir bone mineral density was significantly greater at the

spine compared to stavudine at the end of the 144-week period. For hip, we see no statistical difference, although there was a trend in that direction favoring stavudine.

In randomized, controlled HIV or HBV-infected studies taking Truvada or Viread, the rates of fractures were anywhere from zero to 4.5 percent, which are similar to the control arms, with no drug-related fractures in either study.

In the Partners and iPrEx studies, the fracture rate for Truvada and Viread were roughly 0.5 to 1.7 percent, with no difference compared to placebo.

In conclusion, the overall safety profile of Truvada is well-described, with a low incidence of severity of monitorable adverse events.

In study 903, we did also look at the BMD changes by sex, and we see no statistical difference in terms of the rate of bone mineral density decline by sex. Numerically, the differences in men, the declines in men, were greater, although they were not statistically

different.

In the postmarketing spontaneous adverse reporting rates, we see that the renal events for renal failure and proximal tubulopathy range from 1.1 to 1.6 per 10,000 patient-years. Bone fractures with tenofovir are approximately 0.2 per 10,000 patient-years.

Now we can turn to the data that has been accumulated on Truvada for PrEP indication. Eight studies comprising over 19,000 subjects have been performed to assess the safety and efficacy of oral PrEP. You have already heard today from Dr. Lynn Paxton about the CDC studies, the phase 2 4323 study, as well as the TDF2 study. And she mentioned that the Bangkok study will report results this fall.

In addition, there have been two studies that have been modified, the first of which is the VOICE study. It was modified to discontinue the placebo and tenofovir arms; the Truvada arm is ongoing. Dr. Piper from the NIH will speak to this after the sponsor presentation.

The FEM-PrEP study was presented this March at the Retro conference in Seattle. This study was stopped prematurely in 2011 due to a DSMB recommendation for futility, and I will touch on that briefly.

The study was a randomized, placebo-controlled, efficacy and safety study in three African countries with HIV-negative women at a high risk for HIV acquisition who were not planning to become pregnant. Roughly 1950 patients or individuals were enrolled in the study, randomized one to one to either Truvada or placebo, taken once daily. In April of 2011, the DSMB reported that the study should be stopped because it was unlikely to demonstrate the effectiveness of Truvada in preventing HIV infection.

You see at the top of the slide that the number of HIV infections was similar between the two groups at 33. Notably, in infected cases that matched controls, looking at the percentage of patients with greater than 10 nanograms per milliliter of tenofovir in plasma at study visits,

you see that less than 26 percent of cases or controls consistently had plasma tenofovir levels greater than 10 nanograms per milliliter, indicating that the adherence to study medication was too low to determine whether or not it was effective.

The two studies that anchor today's discussion are iPrEx and Partners PrEP. At this point, Dr. Grant from the University of California at San Francisco will continue our presentation by presenting the background results of a study he led, the iPrEx study, evaluating Truvada for a PrEP indication in MSM.

Sponsor Presentation – Robert Grant

DR. GRANT: Thank you, Dr. Cheng. It's a pleasure to present the primary results for the pre-exposure prophylaxis initiative, or the iPrEx trial. I'm Robert Grant from Gladstone Institutes and the University of California San Francisco.

This was a blinded, placebo-controlled, randomized clinical trial of FTC/TDF chemoprophylaxis for prevention of HIV acquisition

in men who have sex with men. The study was sponsored by the NIH, with co-funding from the Bill and Melinda Gates Foundation, and drug was donated by Gilead Sciences.

I personally receive funding from the NIH, CDC, and in the past, Bill and Melinda Gates Foundation, and the Gladstone Institutes, my employer. This is an independent, nonprofit research organization affiliated with UCSF.

Study drug for the research was donated by Gilead Sciences, but they did not provide funding for the study. Travel to this meeting was funded by the NIH. I have no financial interest in the outcome of the meeting, and I declined honoraria from Gilead.

First I'd like to start with a wakeup call about human immunodeficiency virus, or HIV. Without therapy, this virus kills almost everyone that it infects. It requires lifelong therapy. There is no cure, at least not yet, no clear precedent for protective immunity, and there is no vaccine, at least not yet.

Even with suppressive therapy, this virus causes excess mortality from cardiovascular disease, mortality from malignancies, chronic immune activation, and loss in bone mineral density. This virus infects young people most frequently, before they have a chance to learn to protect themselves in a variety of ways, and as they enter their most productive years. This virus disrupts couples and families and exploits, insidiously, the most human desire for intimacy. By all accounts, HIV is a bad bug.

Men who have sex with men have a 19.3 higher odds of HIV infection. We have known this to be true of our urban centers in the United States for some time; it turns out that it's also true throughout Africa, Europe, Asia, and Latin America.

The rate of new infections in the United States has remained constant over the last 20 years despite widespread knowledge of HIV and the potential for protection from condoms. The rate of 50,000 new infections per year is estimated to be relatively constant since 1991.

We have existing strategies for blocking the spread of HIV, but they have limitations. Condoms must be used during sex, and we know from contraception that the most effective approaches are not linked to sex. Dr. Buchbinder explained earlier how the EXPLORE study showed that intensive counseling was not better than standard counseling.

Male circumcision is a major discovery and advance in the prevention field, and can protect heterosexual men, but it does not protect the rectum. And anal sex is the primary exposure for men who have sex with men, and this practice is reported by 10 to 38 percent of women, depending on the sample.

So this led us to develop the iPrEx study design, which was to randomize men who have sex with men having risk factors for acquisition of HIV, normal renal and hematologic function, and near-normal liver function tests.

They were randomized to receive either once daily co-formulated oral FTC/TDF or a matching placebo, and they were followed for variable

1 periods of time, monthly for HIV seroconversion as
2 the primary outcome. The study was to run and to
3 continue to follow the whole cohort until at least
4 85 post-enrollment infections were observed. A
5 comprehensive package of prevention services was
6 provided to all participants.
7 Primary endpoints and hypotheses of the
8 iPrEx trial were as follows. Efficacy was the
9 primary outcome, analyzed in the modified
10 intention-to-treat population, which included all
11 persons randomized except those with acute
12 infection at enrollment. Acute infection was
13 defined as RNA positive/antibody negative test
14 results.
15 The primary hypothesis was that there would
16 be any efficacy to be evaluated in a two-tailed
17 test. If there was evidence for efficacy, we
18 proposed to evaluate whether the efficacy was
19 greater than 30 percent in a one-tailed test.
20 Safety was the other, secondary outcome of the
21 study.
22 The iPrEx study began enrollment on July 10,

2007 and completed enrollment on December 17, 2009. As of May 1, 2010, the required number of endpoints to complete the trial had been observed, and so this was established by the study sponsor as the primary analysis visit cutoff.

The cohort, however, continued to receive blinded study drug through August of 2010, and then was taken off study drug and followed for an 8-week period after stopped study drug, until November 21, 2010. Two days later, the results of the primary analysis were published in the New England Journal of Medicine.

So the study was fully enrolled as of December 2009 at 11 sites around the world. A total of 2,499 were enrolled. We had study sites in Chiang Mai, Thailand and Cape Town, South Africa who enrolled men who have sex with men in prevention trials for the first time in the history of those continents.

The majority of the study participants were recruited and followed in South America, where the infrastructure for prevention trials in MSM is best

developed. We had two study sites in San Francisco and Boston.

4,906 were screened to enroll 2,499. Thirty-two percent of those screened were found to be ineligible. The most frequent reason for being ineligible was already being HIV-infected. 405 had some other laboratory abnormality, typically elevated AST or ALT or elevated creatinine. Some were at low risk such that intervention like a PrEP was not appropriate. There were individuals who were eligible to enroll but elected not to, typically because they were afraid of side effects of the study drug or they thought the burden of monthly visits was too much for their schedule.

Of those randomized, they were evenly assigned to receive the active and placebo arm. Less than 2 percent had no follow-up HIV test. There were 10 excluded from the primary analysis because they were subsequently found to have baseline acute infection. Those 10 broke down 2 in the active arm, 8 in the placebo arm. Ninety-eight percent of the enrolled cohort was followed for the

primary outcome.

The cohort was young overall, having a median age of 24, which is the age group that is most impacted by new HIV infections in the United States and around the world. Seventy-eight percent had completed secondary education. Nine percent were black, 17 percent white. Sixty-nine percent had mixed or other race. Five percent were Asian. Seventy-two percent had Hispanic or Latino ethnicity, reflecting the South American predominance of the cohort.

Eighty-five to 86 percent of the expected follow-up was completed over the course of the study. The cohort was followed for an average of 1.7 years in both the active and the placebo arm.

The efficacy results, based on the primary visit cutoff of May 1, 2010, was as follows. There was a 44 percent reduction in HIV incidence, having a confidence interval of 15 to 63, 64 infection events in the placebo arm and 36 in the active arm, a statistically significant result at a level of .005.

Containing all of the blinded observation period through August of that same year, the efficacy remained roughly the same, 42 percent, with 83 events in the placebo arm, 48 in the active arm, still statistically significant. In both analyses, the confidence intervals cross, 30 percent, so that we cannot rule out efficacy less than 30 percent in these analyses.

This is the plot of cumulative HIV infection over weeks since randomization. You can see that the curves split early in the course of follow-up and continue throughout. There's no evidence for a change in efficacy over the course of follow-up. P-value for nonproportional hazards was .43. Again, there was evidence of any efficacy at a level of .002, but we could not rule out efficacy less than 30 percent.

This is an analysis of efficacy by subgroup, defined by baseline characteristics. You can see there's trends toward efficacy in subgroups defined by age, level of education, region, Andean versus non-Andean, and alcohol use.

The only significant interaction in the subgroup analysis of efficacy was by baseline reported risk behavior. The efficacy in iPrEx is mainly in those reporting the highest-risk sexual practice, unprotected receptive anal intercourse at baseline.

The subgroup that reported no unprotected receptive anal intercourse did not have clear evidence of efficacy. So this represents an opportunity for targeting this intervention to those who need it the most, those at highest risk of acquiring HIV.

To understand why some people were protected and others were not in the active arm of the study, we performed a case control study of drug exposure and HIV risk that included all active arm seroconverters, defined as cases. These were matched, each one, to three seronegative controls, also from the active arm, and the matching was by site and week of infection.

Viably cryopreserved PBMCs were collected in both groups every 6 months and at seroconversion.

The PBMCs were analyzed for tenofovir diphosphate and emtricitabine triphosphate. Plasma was analyzed for tenofovir and emtricitabine.

Overall, at any given time point, we either see evidence of, one, of no drug or drug moiety, or we see evidence of all four. So we see 95 percent concordance of detection across time points. Either the drug is there or it's not, for the most part.

So this allows us to analyze the percent with any drug or drug moiety detected over time. Time here on the X axis is plotted relative to the visit of first evidence of HIV infection in the cases, and the matched visit in the controls. And on the Y axis, we have the percentage of the active arm that had drug detected.

There are several important features of this data being displayed here. First, in the active arm controls, that is, those who remain seronegative, drug exposure was only detectable in 40 to 50 percent. And this was despite reported adherence that was always over 90 percent as a

median. This indicated over-reporting of adherence, and the drug exposure was detectable in only about half of the active arm seronegative controls.

The proportion with drug exposure among seroconverters was even less, especially around the time of seroconversion, where drug was detected in only 10 percent of the seroconverters at the time of the seroconversion visit or in the time period just before or after -- excuse me -- just before or after the first evidence of HIV infection, which in about 20 percent of the seroconverters was RNA only, as opposed to RNA and antibody.

So drug detection correlated with HIV risk in the active arm of iPrEx. This was analyzed by conditional logistic regression, giving an odds ratio of 16. That was statistically significant, representing a 94 percent reduction in HIV risk associated with having detectable drug. This confidence interval for this estimate ranged from 79 percent to 99 percent.

This kind of analysis can be confounded if

there are factors that link better adherence with safer sexual practices. However, our estimate of HIV risk reduction associated with detectable drug continues to be high, 92 percent, after controlling for age, unprotected receptive anal intercourse at baseline and follow-up, numbers of partners at baseline, body mass index, and schooling.

We became interested in the factors associated with drug exposure in the iPrEx study. These are the three factors of greatest interest and significance. Drug exposure in the United States cohorts was higher, 94 percent in San Francisco and Boston, compared to 43 percent overall drug exposure at sites outside of the United States. This is only in part due to differences in age. We also found that participants over the age of 25 had greater drug exposure than those less than 25, 53 percent drug exposure versus 37 percent.

We had been interested in the possibility that adherence behavior could be linked with safer sexual behavior, so we analyzed the relationships

between these two behavioral patterns, and actually find that those reporting higher-risk sexual behavior were more frequently having drug exposure, 54 percent versus 42 percent among those having sexual partners but no unprotected receptive anal intercourse, versus 38 percent drug exposure among those having no sexual partners in the previous 12 weeks.

So what were the consequences at seroconversion in the active and placebo arms of the study? We do not see a difference in plasma HIV level, not even at the seroconversion visit plotted at week zero here, at a time when reported adherence to study agent was over 90 percent. This provides independent information that drug levels were virologically negligible at the time of first antibody detection in the iPrEx cohort.

Similarly, there was no evidence of drug resistance among those who became infected during PrEP use or after randomization into the PrEP study. On the columns on the right, we have the analysis of seroconverters who were uninfected at

the baseline or enrollment visit, and there was no evidence, genotypically or phenotypically, of FTC or TDF resistance in any of those seroconverters.

Of the 10 who were subsequently found to be acutely infected at baseline, 2 out of 2 had FTC resistance at the seroconversion visit. In both of those cases, seroconversion happened at week 4, and the resistance was confirmed phenotypically. There was one case of FTC resistance combined with resistance to other classes of antiretroviral drugs in the placebo arm; this is a case of primary or transmitted resistance.

Importantly, the two cases of FTC resistance among acutely infected people at baseline were followed over time. The drug-resistant mutant decreases to less than .5 percent of the virus population within 6 months after stopping FTC/TDF PrEP.

Other aspects of safety were evaluated. These were the parameters that required expedited adverse event reporting to the FDA during the course of the study. There was no difference by

study arm in serious adverse events, grade 3 clinical and laboratory abnormalities, grade 4 abnormalities, creatinine elevations as a whole. There was no difference in bone fractures between the active and placebo arm.

There were 9 deaths over the course of the study, only 2 in the active arm, one associated with a motorcycle accident and other associated with a malignancy. The drug was stopped permanently in less than 5 percent, at a comparable rate in the two arms, and temporarily paused at a somewhat higher ate, again comparable between the two arms.

When looking only at clinical adverse events, which were reported in iPrEx if they occurred at grade 2 and above, we see no difference by arm in headache, depression, and diarrhea. And analyzing nausea as a grade 2 and above adverse event, there was no difference between the active and placebo arm. But we know from clinical history that nausea was reported at week 4 more frequently in the active arm, but the reports of nausea

decreased to placebo levels after week 4.

There was a relative increase in the proportion of the cohort reporting unintended weight loss -- this occurred in the first 12 weeks -- and abdominal pain, again mainly a startup syndrome associated with the first few weeks of Truvada use.

There was no difference in elevations in AST, ALT, or total bilirubin. These rates reflect any abnormal laboratory test, most of which were not confirmed on subsequent visits.

Renal safety is a particular concern for this class of drugs. We have here the proportion having grades 1 to 4 creatinine elevations and hypophosphatemia. Creatinine elevations overall were not confirmed on subsequent testing; the table includes all creatinine elevations, even if they returned to normal spontaneously on the next visit. There's no difference in the two arms of the study.

Typically, in the context of clinical trials, creatinine elevations are analyzed just when they are confirmed on a subsequent specimen

collected at a subsequent visit. When we analyze creatinine elevations in this way in iPrEx, we see that there was a total of 8 participants with confirmed creatinine elevations, 7 in the active arm, 1 in the placebo arm.

As of the primary analysis cutoff date of May 1st, 5 of the 7 participants with confirmed creatinine elevations had been observed. All 5 creatinine elevations resolved after stopping Truvada. Four of the 5 were rechallenged with Truvada without recurrence in their creatinine elevation.

There were 2 creatinine elevations that occurred after May 1st. There was not enough time on study to rechallenge those individuals. One creatinine elevation is known to have resolved before entry into the open label phase of iPrEx. The other creatinine elevation occurred in someone who refused further follow-up.

So we evaluated bone safety in a sub-study involving DEXA scanning. This was an opt-in sub-study that enrolled 503 individuals. The opt-in

study was offered in five cities, San Francisco, Rio de Janeiro, Lima, Cape Town, and Chiang Mai. Total body, hip, and spine DEXA scans were performed at enrollment in the sub-study, every 6 months during randomized treatment, 6 months after stopping randomized treatment, at seroconversion, and every 6 months after seroconversion.

The primary results of the DEXA sub-study is plotted here as the average percentage change in the active arm versus the placebo arm in bone mineral density at the spine and the hip, here plotted at week 24, 48, 72, and 96. You can see here that there's an average difference in the active and placebo arm of approximately 1 percent. There's somewhat less. This difference occurs by week 24 and does not progress thereafter.

When we analyze the proportion in the active and placebo arm that reach a clinically relevant endpoint, we see no difference in the placebo and active arm. The clinically relevant endpoint analyzed here is a Z-score on the DEXA scan of less than minus 2. This is defined by the International

Society of Clinical Densitometry as the criterion for low bone mass for age in men having age less than 50. You can see that the overall proportion of the two cohorts, placebo and active arm, reaching this clinically defined endpoint is not different.

We rescanned individuals 6 months after stopping study drug, and found that bone mineral density at the spine and total hip tended to increase in the active arm, again at both the spine and the hip. So there is some recovery in the small change in bone mineral density after stopping PrEP.

The concern about risk compensation is ever-present on our minds. It has been described as the Achilles heel of innovations in HIV prevention. To be sure, this theory assumes a basically rational process in sexual decision making that predicts increased risk behavior if there's decreased perception of HIV risk.

We do not see evidence of risk compensation in the iPrEx trial. In fact, in both the active

and placebo arms, we see a decrease in risky behavior. Here this is the percent reporting unprotected receptive anal intercourse. It decreases from enrollment to week 12, and continues well below baseline throughout the period of follow-up.

We think this reflects ongoing interaction with counselors, provision of HIV testing, and the possibility that taking a pill a day provided a reminder, a daily reminder, of risk of HIV. Condom use increased in the cohort as a whole, again remaining higher than baseline.

We were concerned that reported sexual behavior could be influenced by social desirability bias, so we sought objective measures of HIV incidence that could be compared at enrollment and during follow-up.

This is an analysis of the prevalence of visits having evidence of acute infection, defined as RNA positivity and antibody negativity. The prevalence at enrollment was .4 percent. The prevalence of acute infection decreases in the

placebo arm 3.8-fold to .1 percent. This is commensurate with the trends in reported sexual behavior towards safety. In the active arm, the prevalence of acute infection decreases from baseline 6.5-fold. We think this reflects the added benefits of exposure to FTC/TDF.

So the results of the randomized phase have led us to launch the open label extension of iPrEx, in which individuals are offered open label access to FTC/TDF. They can be followed in the cohort even if they decline to take PrEP.

The aims of this phase of the study, which is sponsored by the NIH, is to provide post-trial access in accordance with the Declaration of Helsinki and good participatory practices to expand the U.S. cohort to include young MSM of color. In particular, we've added a study site in Chicago, which has expertise and experience in following young MSM of color.

We want to listen to PrEP users about implementation issues and to learn how PrEP use changes when people know the tablet is safe and

effective and not a placebo. We want to learn what happens to sexual practices, given this new information, and learn if monitoring for HIV infection every 12 weeks is sufficient to prevent drug resistance.

I wanted to end by reflecting on ways that PrEP to enable treatment initiatives. Clearly, treatment is something that's important for the health of HIV-infected people. It also decreases transmission to their sexual partners.

We do believe that PrEP could enable treatment initiatives in a variety of ways. First and foremost, any prevention strategy that's effective could decrease the burden on HIV treatment programs. We think PrEP in particular could motivate HIV testing, which is the gateway to receiving treatment.

We think it might motivate HIV testing by providing a real benefit to people still hoping that they are uninfected. We also believe that this could lead to seropositives being linked into care in a timely fashion and timely identification

of acute infections, as we have done in the iPrEx study.

PrEP could also create greater familiarity with antiretroviral therapy among a diversity of providers serving a diversity of people. Uninfected people may become more aware of therapy and HIV. And overall, this could help destigmatize therapy and the people who use it to prolong their lives.

So in conclusion, what are the risks and benefits of PrEP observed in the iPrEx study? The risks were nausea and abdominal pain in less than 10 percent, mainly in the first 4 weeks of use; less average weight gain, mainly in the first 12 weeks of use; average 1 percent bone mineral density loss without an increase in the rate of Z-scores less than minus 2; FTC resistance, but only if starting PrEP with preexisting infection. There was no tenofovir resistance, and no resistance at all among those infected after starting PrEP.

The benefits included the following: mainly, decreased HIV infection, with an efficacy

of 92 percent overall and -- excuse me, 42 percent overall and 92 percent if Truvada was used sufficiently to have detectable drug in the body. There was increased HIV testing and counseling, particularly among young people; timely identification of acute infections; decreased partner numbers; more condom use; universal hepatitis B vaccination; routine STI screening and treatment as recommended; antiretroviral treatment and linkage to care.

The intervention also enabled structural interventions at several of our sites; and, I think most importantly, engaged seronegative communities in humanity's struggles to prevent the spread of HIV.

So I'd like to thank the many organizations and people who were involved in making the iPrEx study successful, in particular, Vanessa McMahon, the study coordinator, the hub of the iPrEx wheel; and David Glidden, our protocol statistician. The study was sponsored by the NIH, with co-funding from the Bill and Melinda Gates Foundation, and

drug donated by Gilead. But most importantly, this work was made possible by the 2,499 participants and their communities who believed that research could improve their lives.

So at this point I'd like to turn the podium over to Connie Celum, who'll be discussing the Partners PrEP study, which is complementary to the iPrEx study in many respects.

Sponsor Presentation – Connie Celum

DR. CELUM: Thank you. And it gives me great pleasure on behalf of the Partners PrEP study team to present the results of our trial of antiretroviral pre-exposure prophylaxis for HIV prevention among heterosexual men and women, the Partners PrEP study. I will be introducing the study, and then be followed by my colleague, Dr. Jared Baeten.

First, the Partners PrEP study was funded by a research grant to the University of Washington from the Bill and Melinda Gates Foundation. Study medication was donated by Gilead Sciences. My colleague, Dr. Baeten, and I have received research

funding related to PrEP from both the Bill and Melinda Gates Foundation and the U.S. NIH, but have no other financial conflicts of interest to declare.

So we will first introduce the rationale for evaluation of PrEP in an African heterosexual population. I will describe the design of the Partners PrEP study, and my colleague, Dr. Baeten, will present the primary efficacy and safety results, conclusions, and ongoing activities.

So first, the rationale for evaluating PrEP in an African heterosexual population is, first and foremost, because of the public health priority. Sixty-seven percent of HIV-infected persons globally live in Africa, and 91 percent of new cases of HIV infection globally are occurring in Africa. And although we're making progress in scaling up treatment in Africa and elsewhere in the world, the number of new infections continues to outpace treatment initiation. So we must continue to find new, effective, primary HIV-1 prevention strategies.

Secondly, it was a factor of logistical feasibility. The majority of HIV-1 infections in adults in Africa are heterosexually acquired. So compared to other regions of the world, heterosexual populations at risk for HIV can be readily recruited in high-prevalence African settings.

The rationale for evaluating PrEP in heterosexual HIV-serodiscordant couples is partly of public health relevance in that in Africa and worldwide, a high proportion of new HIV cases occur in coupled relationships. HIV incidence is very high in serodiscordant couples. Past studies have shown incidence rates per year of up to 10 to 15 percent.

Secondly, serodiscordant couples are common. In studies by yourselves and others, we have found that half of partners of a known HIV-infected person are HIV-uninfected. And PrEP offers a strategy under the control of an HIV-uninfected person.

Lastly, the results of this trial are

translatable to other populations. Globally, all transmissions ultimately occur within serodiscordant relationships, and thus our results are relevant to persons at heterosexual risk of HIV.

I just want to reinforce a point that was made earlier, that ultimately, for control of the global HIV epidemic, we're going to need a combination of both primary and secondary prevention strategies integrating both biomedical and behavioral prevention. And to really be effective, what we are looking for are synergies, synergies that can be obtained starting with counseling and knowledge of serostatus, and then interventions that both reduce infectiousness through ART and reduce susceptibility through PrEP, male circumcision, condoms, and behavior change.

The design of the Partners PrEP study was a phase 3 randomized, double-blind, placebo-controlled, three-arm trial of daily oral tenofovir, emtricitabine/tenofovir PrEP for the prevention of HIV acquisition by seronegative

partners in heterosexual HIV-serodiscordant partnerships.

We had two co-primary aims. First, efficacy, to determine if PrEP prevents acquisition among HIV-uninfected persons within HIV-serodiscordant partnerships. And secondly, safety, safety of PrEP when used by HIV-uninfected persons.

The design was that we enrolled 4,758 HIV-serodiscordant couples in which the HIV-seropositive partner was not yet medically eligible for ART following national guidelines. We randomized the HIV-seronegative partners to tenofovir once daily, emtricitabine/tenofovir once daily, or matching placebo once daily. And all individuals in the couple received comprehensive HIV prevention services, and couples were followed up to 36 months.

The trial was conducted in nine sites, four in Kenya and five in Uganda. The procedures were as follows.

HIV-seronegative participants received monthly HIV and, for women, pregnancy testing,

symptom assessment, provision of study medication, and individualized adherence counseling, and every 3 months received laboratory safety monitoring.

The HIV-seropositive participants received every-3-month visits and every 6-month CD4 counts, and throughout the study were assessed for their eligibility for ART, received ongoing HIV primary care, and were actively referred for ART following national guidelines. All participants received a comprehensive HIV prevention package, as outlined below.

So I'll now turn over the podium to my colleague, Dr. Jared Baeten, who'll present the primary efficacy and safety results.

Sponsor Presentation – Jared Baeten

DR. BAETEN: Thank you, and thank you for the opportunity to present these results.

The Partners PrEP study screened 7,856 HIV-serodiscordant couples. For those who did not enroll into the study, the primary reason for not enrolling was that the HIV-positive partner was eligible for antiretroviral therapy based on the

current guidelines for Kenya or Uganda. We randomized 4,758 and followed 4,747.

Enrollment characteristics are as follows. For 62 percent of the couples, the HIV-seronegative partner was the male partner. Thus, for 38 percent of couples, the HIV-seronegative partner was female. The average age of the HIV-seronegative partner was 33 years. Couples reported an average of four sex acts in the month prior to enrollment.

They had been in a partnership for an average of 7 years prior to the time of enrollment, but had known they were serodiscordant for less than half a year, on average. HIV-positive partners had an average CD4 count of just under 500.

Retention in the Partners PrEP study was greater than 95 percent throughout the duration of study follow-up. A total of 7,830 person-years of follow-up were accrued over more than 99,000 monthly visits. Median follow-up for HIV-negative partners was 23 months.

Study medication was dispensed at 96 percent

of attended study visits, and the principal reason for non-dispense of study medication was protocol-mandated hold of study medication due to pregnancy in an HIV-negative woman. Drug holds due to safety were infrequent, accounting for less than 1 percent of follow-up time, and balanced across the three study arms. Based on pill counts of returned unused study product and dispensing records, we estimated that 97 percent of dispensed doses were taken.

During follow-up, HIV-seropositive partners who became eligible for antiretroviral therapy according to the current national guidelines of Kenya and Uganda were actively counseled to initiate treatment, were referred, and were linked to care. During the course of follow-up, approximately 20 percent of HIV-positive partners initiated antiretroviral therapy, and this was balanced across the three study arms.

The study initiated in July of 2008. At an interim review on the 10th of July of 2011, the study's independent data and safety monitoring

board recommended public report of the results and discontinuation of the placebo arm due to definitive HIV protection. The results reported here for our primary data cutoff include all visits that occurred through the 10th of July of 2011.

The primary efficacy analysis looked at an HIV endpoint of seroconversion. The analysis, like the iPrEx study and like the TDF2 study, was a modified intent-to-treat, excluding subjects who were already HIV-infected at the time of randomization. We separately assessed tenofovir alone versus emtricitabine/tenofovir versus placebo, with a one-sided alpha of .025.

During the course of study follow-up, a total of 96 HIV acquisition events were observed through the 10th of July of last year. Fourteen individuals who seroconverted to HIV during the study were retrospectively found to be HIV infected at the time of enrollment. That is, they had seronegative acute infection, and subsequent testing after they later seroconverted on archived samples from their enrollment visit demonstrated

seronegative infection but RNA PCR positivity. Thus, 82 HIV acquisition events are included in the primary analysis. The distribution of these events across follow-up is demonstrated here, showing early and sustained separation between the placebo arm on top in red and the active arms below in blue and green.

In the primary analysis, again there were 82 HIV transmission events. These distribute as follows: 17 in the tenofovir arm, 13 in the emtricitabine/tenofovir arm, and 52 in the placebo arm. This translates into a 67 percent reduction in HIV acquisition in the tenofovir arm, and 75 percent reduction in HIV acquisition in those randomized to emtricitabine/tenofovir. Both of these were highly statistically significant.

The effect of tenofovir and emtricitabine/tenofovir, 67 and 75 percent, were statistically similar to each other, with a p-value of .23. Both tenofovir and emtricitabine/tenofovir ruled out less than 30 percent efficacy -- that is, their lower bound of their confidence interval, or a

formal test against a null hypothesis of 0.7 -- which was the structure under which this trial was designed and monitored.

An intention-to-treat analysis, including the 14 individuals who had seronegative acute infection at the time of randomization, 5 in the tenofovir arm, 3 in the emtricitabine/tenofovir arm, and 6 in the placebo arm -- the intention-to-treat results are similar to the primary modified intention-to-treat results, as highlighted here.

We predefined a subgroup analysis defined by gender. In women, there were 45 HIV infections during the course of the study. This is higher than the number of infections in men, although HIV-seronegative men again made up the majority of those randomized in the study. The distribution of those infections is demonstrated at the top, and their efficacy is here demonstrated in this table.

For tenofovir, efficacy in women was 71 percent, with a p-value of .002. For men, tenofovir efficacy was 63 percent, and the p-value was .01. The far right column is the interaction

p-value, demonstrating that the effect between women and men for tenofovir is not statistically different.

For emtricitabine/tenofovir, efficacy estimate was 66 percent in women and 84 percent in men, both of these statistically significant. And again, in the right column, the interaction is not statistically significant, suggesting, in summary, that both tenofovir and emtricitabine/tenofovir reduced HIV risk in both women and men to a comparable degree.

In additional predefined subgroup analyses based on baseline characteristics, both tenofovir alone and emtricitabine/tenofovir in combination reduced HIV risk in subgroups defined by age, unprotected sex, country of the study site, circumcision status for HIV-negative men, and markers of HIV disease stage in the HIV-positive partner, plasma viral load or CD4 count.

The primary safety results were defined for deaths and serious adverse events, for which there was no statistically significant difference across

the three study arms. A total of 25 deaths occurred in the study, 8 in the tenofovir arm, 8 in the emtricitabine/tenofovir arm, and 9 in the placebo arm. The principal reason for death was trauma. Serious adverse events occurred in approximately 7 percent of study participant and were balanced across the study arms. None of these events were felt to be related to study product.

We monitored renal laboratory safety at month 1, month 3, and quarterly thereafter. For individuals who had abnormal laboratory tests, including renal abnormal tests, laboratory events were repeated for confirmation within 7 days. We found no statistically significant difference in creatinine elevation or phosphorus decrease adverse events across the study arms.

There were a total of 46 grade 1 confirmed adverse events, 16, 18, and 12 in the tenofovir, emtricitabine/tenofovir, and placebo arms. There were a total of 6 confirmed grade 2 elevations in creatinine, 3 in the tenofovir arm, 2 in the emtricitabine/tenofovir arm, and 1 the placebo arm.

For those with grade 2 or higher elevations, all resolved to normal with discontinuation of the study product. For grade 1 events, nearly all resolved to normal with discontinuation of the study product, and nearly all were resumed on study product without subsequent elevations in creatinine. Confirmed phosphorus events were comparable across the three study arms.

We predefined a number of important secondary analyses, including antiretroviral resistance. As demonstrated on the right side of this column, for individuals who were infected -- of this table -- for individuals who were infected after enrollment, none were found to have resistance to emtricitabine or to tenofovir for predefined antiretroviral resistance mutations. This is similar to the iPrEx study and the TDF2 study.

As reported earlier, we had 14 individuals who were HIV-infected at the time of enrollment, but had seronegative infection. Of these, two individuals, one in the tenofovir arm, 1 out of

5, developed resistance, in this case the K65R mutation, conferring resistance to tenofovir. And one individual in the combined arm, 1 out of 3, developed resistance, in that case the M184V mutation, resistance to emtricitabine.

For context, we also analyzed other antiretroviral resistance. Four individuals across the three study arms were found to have mutations conferring high-level resistance to non-nucleoside reverse transcriptase inhibitors, either K103N or V106A. This resistance is unlikely to be selected by the study medication, and instead reflects transmitted resistance, that is, resistance circulating as a result of treatment.

Like the iPrEx study and like the TDF2 study, we analyzed the relationship between tenofovir levels and HIV protection. We performed a case cohort analysis, limited to the tenofovir and emtricitabine/tenofovir active arms. We measured levels of tenofovir in plasma. For our cases, like the other studies, we selected individuals who seroconverted to HIV, and we

specifically looked at the seroconversion visit as well as visits prior to seroconversion.

For our cohort, we selected individuals who remained HIV-uninfected during the course of the study, 100 from each of the two active arms. We selected longitudinal samples from across their study follow-up, both early and late in follow-up.

In total, approximately 1,000 plasma samples were tested, and these are the results. In individuals who remained uninfected during the course of the study, 82 percent of time points demonstrated detection of the study product. In contrast, for individuals who seroconverted to HIV, tenofovir was detected at 31 percent of seroconversion visits, considerably less, and at 56 percent of visits prior to seroconversion, also less.

When calculated together, the relative risk reduction associated with detectable study product was 86 percent for tenofovir in the tenofovir arm and 90 percent in the emtricitabine/tenofovir arm. Both of these were highly statistically

significant.

We collected additional objective adherence information in a sub-study looking at objective measures of adherence. This study was implemented in 2009 after the main trial had already begun, and it used MEMS caps, or electronic monitoring pill bottles, monthly then transitioning to quarterly home unannounced pill counts, as well as home blood draws, which have not yet been analyzed. There was a counseling intervention implemented for those with unannounced pill count adherence less than 80 percent.

This sub-study involved 1147 HIV-uninfected partners who were part of the larger main trial. The objective measures of adherence were consistent with our other reporting of adherence in the study, that median unannounced pill count adherence was 99 percent in the sub-study population and median MEMS adherence was 92 percent.

In individuals who were participating in the sub-study within the larger trial, there were a total of 14 HIV infections observed during their

participation in the sub-study. All 14 were among individuals who had been randomized to placebo. None were among individuals who had been randomized to active PrEP. Thus, it emphasizes that high adherence in the setting of active adherence monitoring and support was associated with a high degree of reduction in HIV risk.

Because we enrolled HIV-negative women in the study, we monitored for pregnancy. A total of 288 pregnancies were observed in the study through July of last year. Pregnancy incidence was 10 percent per year and was comparable across the three study arms.

Of the 288 pregnancies, 262 had gone to completion by the end of January of this year, in supplemental data sets provided as part of this application. The remainder of pregnancies had not yet completed because they had been detected in late June or early July and had not been completed by January.

Sixty-four percent overall of pregnancies ended in live births, and this was statistically

similar across the three study arms. Importantly, 93 percent of pregnancy losses were at less than 20 weeks' gestation. This was in large part because of pregnancies that were detected as a result of monthly scheduled pregnancy testing, and would have been pregnancies that would likely have not otherwise been detected by a woman or her partner.

Eighteen of 95 pregnancy losses were reported as induced losses, although this number may be an under-report given legal restrictions on pregnancy termination in the countries where the study was done.

We analyzed sexual behavior over time. At the time of enrollment, 27 percent of couples reported unprotected sex in the prior month. This declined during study follow-up to approximately 10 percent per month and was stable, and this was similar across the three study arms. So condom use increased during the study.

I would like to take a minute to describe the next steps in the Partners PrEP study. As

described earlier, in July of last year the data safety monitoring board of the study recommended discontinuation of the placebo arm. Thereafter, the active arms were continued, and the placebo arm was re-randomized to active PrEP, to one of the two PrEP active arms.

This is allowing us to collect additional comparative data on safety and efficacy of single versus dual drug pre-exposure prophylaxis, as well as sexual behavior, pregnancy incidence, and other information, especially in the context of known efficacy and known receipt of active PrEP.

We have thought considerably about the interrelationship between PrEP and treatment for HIV-serodiscordant couples because both have been demonstrated to provide substantial protection against HIV infection. For both, of course, protection is likely highly related to adherence. And for HIV-serodiscordant couples, it is important to recognize, based on studies we and others have done, that 25 to 30 percent of new infections can occur from outside partnerships.

We and others have looked at mathematical modeling to try to guide the use of antiretroviral therapy and pre-exposure prophylaxis for implementation, and we have looked at this specifically in couples and have considered the possibility of pre-exposure prophylaxis as a bridge until ART is initiated and viral suppression achieved in the HIV-positive partner.

We recognize that PrEP is under a strategy that is under the control of an HIV-uninfected person whose partner declines ART, does not want to initiate ART at this time, or whose HIV status is unknown.

With this in mind, in addition to continuing the Partners PrEP study with active study medication, we'll be initiating an open label demonstration project of pre-exposure prophylaxis in serodiscordant couples, recruiting those couples who are highest risk for transmission, offering onsite or referring for antiretroviral therapy for positive partners according to national guidelines.

For those who accept antiretroviral therapy,

we'll use time-limited pre-exposure prophylaxis as a bridge to viral suppression in the positive partner. And we will extend pre-exposure prophylaxis for negative partners in couples which the positive partner does not initiate ART, declines ART, or is not yet eligible.

Thus, in summary, in the Partners PrEP study, tenofovir and emtricitabine/tenofovir pre-exposure prophylaxis provided 67 and 75 percent protection, respectively, against HIV acquisition among heterosexual men and women who were at risk for HIV infection because of a known seropositive partner when provided in the context of other prevention services. HIV protection in our study was robust in both women and in men.

We saw a similar frequency of key safety parameters for those randomized to PrEP versus placebo. Resistance to emtricitabine or to tenofovir was detected only in individuals with acute HIV infection at the time of PrEP initiation, and in that case, only in 2 of 8 individuals. And we saw no evidence of behavioral risk compensation.

The Partners PrEP study was conducted by a large collaborative team from the University of Washington and sites in Kenya and Uganda. The study was funded by the Bill and Melinda Gates Foundation, and study drug was donated by Gilead Sciences. We are grateful to the HIV-serodiscordant couples who tested, screened, and participated in the study.

Thank you. I will now hand back to Dr. Cheng.

Sponsor Presentation – Andrew Cheng

DR. CHENG: In order to support the use of Truvada for pre-exposure prophylaxis, Gilead Sciences proposes to implement a rigorous and comprehensive risk evaluation and mitigation strategy comprised of three key components.

Safety data on Truvada for PrEP will be collected as part of the ongoing, existing routine pharmacovigilance program. However, additional pharmacovigilance activities will be implemented for Truvada for PrEP.

A formal REMS, a risk evaluation and mitigation strategy, which will provide

comprehensive education and information emphasizing the importance of three key components -- that PrEP is part of a comprehensive HIV prevention strategy; regular HIV testing before initiation and regularly while on PrEP; provider assessment for acute HIV infection prior to starting and continuing in PrEP.

The risk evaluation and mitigation strategy will focus on educational outreach. The specific components of this program will include a notification letter to healthcare providers on details of PrEP; full prescribing information; a MET guide with every bottle of Truvada; training for healthcare providers; prescriber and individual safety brochures; and a Truvada wallet card. All materials will be available online as well as hard copy.

In addition to the pharmacovigilance and REMS, Gilead will also provide free HIV and HBV testing, free condoms, subsidize HIV viral resistance testing to those who seroconvert, an opt-in reminder service regarding regular testing for HIV infection, HBV, and other STDs.

In addition, there will be a voluntary participation of individuals and prescribers in the Gilead PrEP registry project; support for community education activities related to PrEP, for example, CDC interim guidance for PrEP in MSM; and a medication assistance program for Truvada for PrEP indication for individuals who lack prescription coverage.

The CDC released their interim guidance, as Dr. Paxton indicated earlier, on healthcare providers addressing the issue of PrEP for the prevention of HIV infection in MSM in 2011. These would be emphasized in the community education projects.

Data are continuing to accrue in both MSMs and serodiscordant couples in a variety of other initiatives. In terms of the ongoing and planned phase 3 before research, including demonstration projects, there are roughly 30,000 participants in 22 different studies. These are postmarketing demonstration studies in the U.S. and globally and involve collaborators, as listed here.

These ongoing studies and an informed decision today will allow Gilead Sciences to provide comprehensive support for the use of Truvada for a PrEP indication, which will lead to a positive public health impact. As mentioned earlier, the impact of PrEP supports the goal of reducing HIV infections as part of the White House National HIV Strategy.

What will PrEP give us beyond what we have now? It will add to a combination of behavioral interventions, partner services, and expanded testing and treatment that could, together, drive incidence lower, enough to be reversing the HIV epidemic. It could also provide an incentive to individuals and healthcare providers to test for HIV.

It would be an additional female-controlled method, and it would offer men and women a proactive prevention modality that is not completely dependent on the partner's behavior, thereby empowering HIV-negative individuals at risk for HIV to protect themselves.

Dr. John Mellors will now share his perspectives and commentary on this data set and the public health impact of Truvada for PrEP.

Sponsor Presentation – John Mellors

DR. MELLORS: Good morning. Thank you, Andrew. It's a real pleasure to speak today on this most important day in HIV prevention, and to be able to summarize the data that you've just heard.

By way of disclosure, I'm the director of the virology core laboratories for the Microbicide Trials Network, and the AIDS Clinical Trial Group funded by NIAID. I also receive other funding from NIH. I've been a member of the Scientific Advisory Board at Gilead Sciences since 1998, for which I receive annual compensation. But I have no financial interest in the outcome of this meeting.

What I'd like to cover with you in the next few minutes is to review the rationale and human efficacy data, highlighting the importance of drug exposure and adherence; to review safety overall and in special populations; to address other key

issues, particularly HIV drug resistance and risk compensation; and present some modeling studies on the potential for public health benefits, specifically in the Washington, DC area and the epidemic there; and then with some final considerations for the panel.

First, some historical perspective. Three days before the tragedy in New York on 9/11, we were presented, as members of the Gilead Scientific Advisory Board, with the idea of using FTC/tenofovir for HIV prevention.

The rationale presented is that both are potent inhibitors of HIV. They protect uninfected cells from infection. They penetrate well into sites of exposure. Their pharmacokinetics allow once-daily dosing. And they had a good safety and tolerability profile for treatment. The board enthusiastically recommended that the program be launched. And what you've just heard is the culmination of those efforts.

In terms of human protective efficacy, they are summarized here: iPrEx, overall 44 percent

reduction; Partners PrEP, 75 percent reduction, 84 percent in men and 66 percent in women; the TDF2 trial presented by Lynn Paxton, 62 percent reduction; the FEM-PrEP trial was stopped for futility; and the VOICE study continues with a comparison of FTC/tenofovir versus placebo, and we hope to hear results soon.

This slide highlights the importance of drug exposure and adherence on efficacy. In iPrEx, 92 percent in subjects with detectable drug levels; 90 percent in Partners PrEP; 78 percent in CDC TDF2, excluding subjects with no refills for more than 30 days; and in FEM-PrEP, stopped again for futility, 6 percent point estimate, but less than 26 percent had consistently detectable drug levels, and the conclusion was that adherence was too low to assess efficacy.

So to summarize the human efficacy data, it's been demonstrated in high-risk MSM in iPrEx; in heterosexuals in Partners PrEP; TDF2 in men, in iPrEx, Partners PrEP, and TDF2; and in women in Partners PrEP and TDF2.

Efficacy is strongly associated with adherence and drug exposure, and that underscores the importance of education, careful screening, adherence, and behavioral counseling in any rollout program. We've also seen that not all infections on PrEP are associated with non-adherence, and further research is needed to define the threshold exposure necessary for HIV prevention.

In terms of safety, the overall safety for iPrEx was similar between the active arm and the placebo, with the exception of more GI events through week 4. In Partners PrEP, similar safety across all arms. Discontinuations for safety or intolerance were rare in both trials and not different between placebo and active arms.

In terms of renal safety, there are mild or moderate serum creatinine elevations at a similar frequency in iPrEx, and they were infrequent in Partners PrEP and not different across arms. For bone safety, there was a reduction in bone marrow density, but not to clinically significant levels in the iPrEx study, with a return towards baseline

with product discontinuation. There was no increase in fractures in the Partners PrEP study.

So moving on to special populations, the safety profile in women is similar to that in men in Partners PrEP. We heard a little bit about the BMD data from TDF2 that was combined. I would be interested further to see the differentiation between men and women, but Lynn Paxton reassured us that there was no difference. There's also a large study as part of the VOICE trial, VOICE-B, that will look at bone mineral density throughout that trial.

In pregnant women, in Partners PrEP the birth outcomes, as Jared Baeten showed you, were similar for women on PrEP or placebo. In the antiretroviral pregnancy registry, prevalence of birth defects after tenofovir or FTC exposure were low and similar to prevalence in the general population. And in clinical studies of HIV in pregnant women, there's no increase in congenital abnormalities with in-utero tenofovir or FTC exposure.

In terms of adolescents, there's a bit of a knowledge gap here because PrEP studies only evaluated subjects greater than 18. FTC/tenofovir is currently approved for treatment of individuals 12 years of age and older, and we look forward to the ATN studies 110 and 113, which will evaluate the safety of PrEP in adolescents 15 to 22 years.

In patients with mild renal impairment, recall that PrEP studies only evaluated patients with baseline creatinine above 60 milliliters per minute. Data from 903 and 934 treatment studies demonstrated no increased risk of renal events in patients with mild renal impairment.

Now, these data are positive and reassuring, but there's clearly a need for longer-term safety studies. And that involves continued monitoring and expanded safety database. That will be achieved through standard pharmacovigilance and reporting, and demonstration projects in the U.S. and the rest of the world. Those are summarized on the next slide.

They will focus on renal, bone, adherence,

risk behavior, STIs, drug levels, and drug resistance monitoring; 14 studies in MSM, eight studies in heterosexual men and women and serodiscordant couples, for over 32,000 total subjects followed.

In terms of HIV drug resistance, a topic near and dear to my soul, it's clear from the data that there were infrequent cases of drug resistance among PrEP study participants who seroconverted while receiving active drug. I'm going to talk later on about those who were infected on enrollment, but this is just individuals who seroconverted on PrEP.

None in iPrEx. None in Partners PrEP. In TDF2, one in the placebo arm. In FEM-PrEP, we have incomplete information; there were 68 infected. One in the placebo arm had 184V transmitted drug resistance, most likely, and four in the FTC/TDF arm.

Lut Van Damme, myself, Bob Grant, Teri Liegler, who performed all the studies, have reviewed each of these four cases, and we feel that

one is probably transmitted drug resistance, two possible, and the last one likely to have had incubating HIV infection at enrollment.

So why is drug resistance infrequent? Well, the risk of seroconversion and drug exposure are inversely related. If there's no or low drug exposure, there's no selection by drug, no resistance, but there's infection. If there's good exposure, there's no infection, and consequently no resistance.

Resistance is still possible, however, at drug exposures that permit infection but also provide selection of resistant variance. So far this appears to be uncommon. What I've just said is complicated, so I'd like to illustrate that further with some graphics.

So here is a graphic showing the theoretical relationship between infection, drug exposure, and resistance. On the X axis is drug exposure, going from low to high, and on the Y axis is the fraction infected or infected with a resistant virus. The blue line is the proportion infected, and the red

line, dashed, is the frequency or proportion with resistant virus.

The box shows where there's no drug exposure. As I said, with no drug exposure, no resistance, but the consequence is infection. The middle zone is the zone of resistance risk. It's a theoretical zone. We don't know how narrow it is or how broad. It seems at first approximation to be narrow. This is the zone where there's an adequate exposure to select for resistance and partial protection.

The far right zone is the zone we've seen most frequently in Partners PrEP in about half of individuals, in iPrEx, where there's sufficient drug exposure, no infection and no resistance.

Resistance is more likely if PrEP is given during an unrecognized acute infection. And this is because infection and incomplete suppression of replication by two drugs, FTC and tenofovir, selects resistance. In iPrEx, two of two in the active arm developed 184V or I mutations. In Partners PrEP, two of eight, one with 65R, one with

184V. In TDF2, one of one who received active drug developed triple mutant. And in FEM-PrEP, zero of one, who randomized to the active arm, received or acquired resistance.

Some other considerations about resistance. 65R and 184V or I mutants are likely to decay rapidly to low levels off PrEP because there's a fitness advantage for the virus compared with wild type in the absence of drug selection. This has been observed, as pointed out by Dr. Grant, in cases followed off PrEP and also in FEM-PrEP.

Low-frequency variants -- meaning once the virus decays to low levels -- low-frequency variants are unlikely to be transmitted on a probability basis because we understand the biology of transmission to involve one variant, and that's much more likely to be a dominant variant than a minor variant. The impact of such low-frequency variants on response to FTC/TDF containing ART is uncertain. Other ART regimens, however, are likely to be effective, those containing PIs or integrase inhibitors.

Some additional points are that the 65R mutation is hypersusceptible to AZT, and the 184 mutation is hypersusceptible to both tenofovir and AZT.

So summarizing resistance, it's most likely to occur in persons already infected, so we must screen and monitor for infection. It's infrequent but still possible while on FTC/tenofovir, so we must monitor for infection and discontinue PrEP with any evidence of infection. And resistant virus is likely to decay off PrEP, resulting in low transmission risk.

In terms of risk compensation -- I won't spend a lot of time on this -- there's no evidence of increased risky behavior while receiving either active or placebo in iPrEx or Partners PrEP. So it's not been observed in well-conducted clinical trials. There's clearly a theoretical risk in less structured settings, again underscoring the importance of education, careful screening, individual risk assessment, adherence, and behavioral counseling.

In terms of public health benefit, I engaged Tim Hallett from the Imperial College and Ruthie Birger to model the potential impact of PrEP on the HIV epidemic in the Washington, DC area. Ruthie Birger is from Princeton University. And we were helped by Alan Greenberg at George Washington University, who helped us provide DC public health data.

The modeling methods are straightforward, deterministic, compartmental ODE model that captures three disease stages: awareness of infection, treatment status, multiple risk groups for men and women, including heterosexual, homosexual, bisexual, and injection drug use.

The natural history parameters and population characteristics were from the literature, but importantly from the DC Health Department. The model was calibrated first to DC data based on prevalent infections with Bayesian methodology.

Everyone in the population was considered to have the same chance of being enrolled in a PrEP

program. A fraction were assumed to adhere well, achieving a 90 percent reduction in infection from sexual exposure, and the remainder assumed to be poor adherers, receiving only 15 percent benefit. PrEP was assumed to have no efficacy against parenteral exposure because that efficacy has yet to be demonstrated. Scale-up began in 2012, and reached peak coverage in 2015.

Here is the output -- excuse me. There are two scenarios modeled: good adherence, in which 70 percent of individuals are good adherers; and poor adherence, in which only 30 percent of individuals are good adherers. And I'll show you a range of outcomes, and that's due to uncertainty and imperfect knowledge of patterns of risk behavior. The impact is compared to ART. Treatment is 60 to 70 percent of those in care, without any other intervention.

Here is the calibration of the model against data. The data points by risk group are shown as dots, large dots, and the model output is shown as lines.

Here is the model output for the 70 percent good adherers. On the Y axis is the absolute number of infections prevented, and across the X axis is the proportion of the population that's covered by PrEP. And you can see over a 10-year period, over a thousand infections can be prevented, with a broad range of output because of uncertainty. With 30 percent good adherers, there's still an effect, but it's attenuated.

So this model shows that the protection and public health benefit is proportional to coverage of the population and adherence. And there's a linear relationship.

There are many other supportive models of PrEP rollout without risk compensation, or inadvertent use in HIV infected can decrease transmission and prevalence of drug resistance. This work was pioneered by Professor Blower, who's on the panel, as well as by colleague, Dr. Abbas, at Cleveland Clinic.

There are also several models showing that PrEP is cost-effective when targeted to the

highest-risk groups: Kamal Desai, Rochelle Walensky, Tim Hallett, and most recently Juusola, et al. in the Annals of Internal Medicine showing the cost-effectiveness of the intervention.

So let me end by reviewing considerations for approval and considerations against approval. First consideration. The U.S. annual HIV incidence is unchanged in 15 years, at about 50,000 new cases. So new interventions are clearly needed.

Many interventions that have been studied as primary prevention have been ineffective in clinical trials. Professor Nancy Padian, who's on the panel, reviewed this very nicely in an article published in AIDS in 2010.

FTC/TDF can prevent infection when added to existing prevention methods. Its efficacy depends on drug exposure, summarizing that by, if taken, it works. It's generally well-tolerated, has a favorable safety profile. Long-term safety surveillance is planned, including the special populations that I mentioned in the demonstration projects.

HIV drug resistance appears to be infrequent, but we must in any program exclude acute or chronic infection. Individual and public health benefit is possible, and PrEP programs, as illustrated by Dr. Grant in iPrEx, could well lead to increased HIV testing. And I don't think there'll be any argument about the importance of widespread HIV testing in controlling the epidemic.

Considerations against approval that I've heard are the efficacy in iPrEx was modest. But let me remind you once again, it's 92 percent in individuals with detectable drug levels.

It's only effective if taken. Well, that's not a surprise because that's true for antihypertensives, cholesterol-lowering agents, and all preventive or therapeutic antimicrobials.

Those who need it most won't take it. Well, actually, Bob Grant showed you nice data, greater risk perception, greater adherence in iPrEx.

There are adverse events. Well, FTC and TDF is well-tolerated in trials, with a safety profile

similar to placebo. Monitoring is planned in open label projects and through the REMS. The bone mineral density losses that have been observed are clinically insignificant, but we await further data in the female population.

HIV drug resistance is a concern, but so far it's been infrequent and, I believe, manageable by screening and monitoring for infection.

Then the concern about risk compensation. No evidence in placebo-controlled trials, and there are plans, as mentioned, to monitor in open label projects.

So in closing, existing interventions have not reduced the number of new infections in the United States annually, and new measures are clearly needed. The greatest potential for benefit is in men or women at high risk of HIV infection who are motivated to protect themselves and who have no control over antiretroviral use in their partners.

I believe the maximum potential benefit will not be realized without approval for a PrEP

indication coupled with programs that support education, screening, adherence, and behavioral counseling and monitoring.

Finally, FTC/tenofovir could provide an effective, additional means of preventing HIV infection and lowering HIV infection both in the U.S. and worldwide, which is the goal of all of us in this room.

Thank you.

DR. CHENG: I wanted to highlight that these additional individuals are available to answer questions from the panel, if needed.

Clarifying Questions from the Committee

DR. FEINBERG: I imagine there are a fair number of questions, and so I think what I would like to do to begin with is just start at Dr. Robinson's end, go around the table, and then you can raise your hand and we'll go in order after that. I think there's probably a lot to ask.

DR. ROBINSON: Okay. Patrick Robinson. Thank you for starting at this end so nobody supervenes my question with theirs.

A two-part question on risk behaviors. We've heard that there is significant concern about the reliability of adherence reporting. Risk behaviors are also self-reported in these trials. So what is the level of confidence among the conductors of the trials that the reported risk behaviors are actually reflecting reality?

Part two is, if this is indeed reality, it's a reality set in a very controlled clinical trial situation, what is the expectation for non-controlled risk behavior changes?

DR. CHENG: Thank you very much. Since your question is a two-part question, I'll ask that Dr. Grant and Dr. Baeten come to address the confidence of the risk evaluation to adherence in each of their studies, and then we can address part two.

DR. FEINBERG: Before we proceed, I just want to remind the panel members that this part of the meeting is for asking clarifying questions of the data that have been presented. Later, when we address the questions, there'll be a broader

opportunity to converse about this.

DR. GRANT: We would not want anyone to conclude from our data that self-report or reported behavior should be dismissed in all circumstances. I think that social desirability bias is a potential factor in what people tell us about what they've done.

In the case of adherence, the socially desirable response is clear. We recommended daily dosing. People consented to attempt daily dosing. Good adherence is daily dosing. The social desirable bar is clear. And people did tend to over-report adherence in iPrEx. In the case of sexual behavior, the socially desirable response is less clear. We do know that some people, in fact, exaggerate their sexual behavior.

We do have two objective measures of reducing risk. In the context of the iPrEx trial, I presented the acute infection prevalence, which decreased 3.8-fold in the placebo arm, reflecting the comprehensive package of prevention services that was provided.

Now we have slide up. We also have evidence from syphilis rates in iPrEx, which the incidence of new RPR-positive syphilis cases was running approximately 3 percent toward the beginning of the study, and it decreases over the course of the study, of iPrEx in both the active and the placebo arm.

So we do have some objective correlates of decreasing risk, sexual risk, in the context of iPrEx.

DR. BAETEN: In the Partners PrEP study, I think we would have a very similar set of information as they have in iPrEx.

The first would be to look at our placebo arm, where it is important to recognize that HIV incidence was 2 percent per year. In the absence of ongoing HIV testing or behavioral risk reduction, HIV incidence in serodiscordant couples has been documented to be 10 to 15 percent per year. So our PrEP strategy, which reduced HIV incidence to a half a percent per year, was additive beyond the other strategies that were

being done.

Secondly -- slide up, please -- like in iPrEx, we measured sexually transmitted infections at baseline and then during the course of follow-up, and demonstrated that the prevalence of sexually transmitted infections, in this case curable STIs -- syphilis, gonorrhea, chlamydia, trichomonas, or symptomatic genital ulcer disease -- decreased from the prevalence detected at enrollment to the prevalence as detected through the first year, the second year, or the third year of follow-up. And these were comparable across study arms, but were also decreasing during the course of follow-up.

Then finally, from other studies that we have done, observational studies in the absence of placebo-controlled intervention, we have seen that HIV-serodiscordant couples report higher use of condoms and reduced sexually transmitted infections after becoming aware of HIV serodiscordancy and in the presence of ongoing HIV testing.

DR. FEINBERG: Can I please also ask the

respondents to the questions from Gilead, if you weren't one of the prior speakers, can you tell us your name and your responsibility. Thank you.

Let's go.

DR. RUIZ: Monica Ruiz, George Washington University. Thanks to everyone for a tremendous amount of information.

My question is to Dr. Cheng with regard to the REMS that you've presented, the risk evaluation and mitigation strategy. Could you please clarify the intention of the Truvada wallet card? Everything else made sense to me, and perhaps that was in the CD-ROM materials, but I must have missed it. And I was wondering if you could expand on that a bit.

DR. CHENG: Sure. I'd like to ask Dr. Peschel to come speak to that.

DR. PESCHEL: My name is Dr. Tobias Peschel. I'm vice president of drug safety and public health for Gilead Sciences. Slide up, please.

The wallet card is really part of the education that's directed at the patient directly.

It's a credit card-sized card that the individual can carry with them at all times. And as it states here, it includes brief information about, basically, the key safety risk messages -- the negative HIV test is critical -- the recommended daily dosage, and the importance of taking Truvada only as part of a comprehensive regimen.

Next slide up, please. This is just a snapshot of what it will look like. Slide down.

DR. PADIAN: Nancy Padian, UC Berkeley. I have a question for Bob that actually is relevant for Connie and Jared, and that is, when you showed infection rates by age, I wondered -- that was slide 37. You have enough people, I think, in the 18- to 21- -- I don't know where Bob is -- in the 18- to 21-year-olds that you could disaggregate that.

The reason why I thought that was important is that you made the good point that they were at highest risk. And also, you can see both there, and also on the slide when you look at the amount of drug detected, that the amount of drug detected

also was somewhat less in the under-25s. And there, too, could you disaggregate that into just what was going on with the 18 to 21s?

Similarly, in Connie's study, there was a little bit -- could you also look at the younger women, younger than 25?

DR. GRANT: This was the result of a prespecified subgroup analysis. We have not completed additional analyses breaking down this subgroup into quartiles of age. This represented above and below the median age.

So I think that additional studies in very young people, between the ages of -- well, 18- and 19-year-olds and even younger -- would need to be done to increase our confidence that this -- increase our confidence and experience with PrEP in this group.

DR. BAETEN: Thank you for the question. We had -- in Partners PrEP, about 15 percent of the total population was under age 25. So it's difficult to do subgroup analyses in that.

For your specific question, though, for

younger women, which I believe you asked, we have done an analysis that -- I don't have a slide on because it was not prespecified, but we have recently done an analysis in women under age 30, which is 600 women total in the population.

There were 4 infections in the tenofovir arm, 5 infections in the emtricitabine/tenofovir arm, and 17 in the placebo arm. Placebo arm instance is 6 percent per year, 6.1 percent per year. The efficacy estimates are 78 percent for tenofovir, 72 percent for emtricitabine/tenofovir. The p-values are .01 for both of them.

DR. PADIAN: Thanks. Can I ask another one?

DR. FEINBERG: Yes.

DR. PADIAN: Thank you. I'm still Nancy Padian from Berkeley. And I have a question about Tim's model. Maybe it's completely obvious and I don't know if you even could answer it.

That is, in the scenario with the poor adherers, did he take into account -- because 10 years is a pretty long time -- so did he take into account onward transmission of people who

became infected? I mean, were you looking at it sort of as a cohort, or was it a dynamic model? Were you able to look at onward transmission?

DR. CHENG: I believe Dr. Hallett is on the phone. Is that correct?

DR. MELLORS: We have to ask permission.

DR. CHENG: Oh, excuse me.

DR. MELLORS: Madame Chairperson, can we pipe Dr. Hallett in?

DR. FEINBERG: Yes.

DR. MELLORS: That's the administrative obstacle. How about the technical obstacle? Are we ready to go?

I believe, while we're getting Dr. Hallett, it is a dynamic model that takes on secondary transmissions.

Dr. Hallett?

DR. HALLETT: Hello?

DR. MELLORS: Hey, Tim.

DR. HALLETT: Hello?

DR. MELLORS: Tim, this is --

DR. HALLETT: Am I coming through?

DR. MELLORS: Yes. You have a question from Dr. Nancy Padian --

DR. HALLETT: Sure.

DR. MELLORS: -- about the DC model. Does it model secondary transmissions, i.e., is it a dynamic cohort model?

DR. HALLETT: Yes, it is. It's an dynamic translational model. So it captures the prevention benefit of PrEP to the individual taking PrEP, and all indirect secondary benefits which stem from that.

DR. MELLORS: Thank you. I feel like you're on "Who Wants to Be a Millionaire," and you're a lifeline.

(Laughter.)

DR. FEINBERG: Okay. Dr. Cheever?

DR. CHEEVER: Laura Cheever from HRSA. Two questions.

One, in the iPrEx study, I saw that you had excluded people that weren't considered to have significant enough risk to enroll in the trial. And just what was your cutoff for risk?

DR. GRANT: The definition of risk that was allowed for eligibility in the trial was as follows. Slide up.

No condom use. A report of no condom use during last anal intercourse with a male HIV-positive partner or partner of unknown status in the last 6 months prior to screening. Anal intercourse with more than three male sex partners in the last 6 months. Sites could apply more restrictive criteria and require five or more male sex partners in the last 6 months.

Exchange or transactional sex. Sex with a male partner and an STI diagnosis in the last 6 months or at screening. And a sexual partner of an HIV-positive man with whom condoms were not consistently used in the last 6 months.

So these were the criteria. If individuals met any of these criteria, they were eligible based on risk. These have been applied in a variety of different prevention trials and shown to be associated with high HIV incidence.

DR. CHEEVER: And I had a second question

that maybe should be deferred to later if it's not appropriate here. And that was that in the Partners trial, they talked about 20 percent of partners were referred to ART. And if we had the information about if the partners were on ART and undetectable, what the relative efficacy was of PrEP for placebo versus treatment arm.

DR. BAETEN: Slide up, please. So in Partners PrEP, again, 20 percent of the HIV-positive individuals initiated combination antiretroviral therapy during the course of the study. We examined whether that had any effect on the primary efficacy results and excluded seroconversions that occurred among partners after their HIV-positive partner initiated antiretroviral therapy.

There were only 5 such infections, 3 in the tenofovir arm, zero in the combined emtricitabine/tenofovir arm, and 2 in the placebo arm, although the amount of follow-up time available for this is quite small because, obviously, antiretroviral therapy was not initiated until after people were

already in the study for some period.

All five of these infections occurred in the first three months after report of antiretroviral use by the positive partner. Exclusion of those events does not influence the primary efficacy estimates. They're 72 percent for tenofovir and 75 percent still for emtricitabine/tenofovir.

DR. CHEEVER: Thank you.

DR. FEINBERG: Dr. Kuhar?

DR. KUHAR: Yes. David Kuhar. And I am not sure if I just missed this or if this was said.

But in the iPrEx trial, among the ineligibles, about a third were ineligible due to other reasons. And I was just wondering if you presented what some of the other reasons were.

DR. GRANT: Other reasons. Slide up, please. So the study site was given broad discretion to exclude individuals who they felt that alcohol or drug use was considered sufficient to hinder compliance with study procedures. Typically, these are people who presented in a way that made it unclear that they could consent for

the protocol, or that they knew that they would be able to commit to completing study procedures.

The study also excluded people with serious and active infections. Active tuberculosis, for example, would have been considered an exclusionary criteria. If individuals could not provide an address for personal contact to allow regular follow-up; if they were unwilling or unable to provide blood or urine specimens; if there were positive urine dipsticks that were consistently positive for glycosuria or proteinuria; acute hepatitis B infection.

Only eight were excluded for contraindicated medications; typically, these were antibiotics or other agents that are known to be nephrotoxic; if they couldn't speak the local language, or if they were too young. A variety of other things.

DR. KUHAR: Thank you.

DR. FEINBERG: Dr. Giordano?

DR. GIORDANO: For Dr. Mellors, you commented -- I believe it was presented that in the iPrEx study, deep sequencing for resistance was

done. But I'm not sure if that was done in the Partners PrEP study. Could you clarify that, whether that was done or not?

DR. MELLORS: John Mellors speaking again. I'd invite Bob Grant to come up and show us a little specific PCR results from iPrEx. In Partners PrEP, it was not performed, but is planned.

DR. GRANT: Thank you, John. We did do allele-specific PCR analysis for minor drug-resistant variants in the iPrEx study. Slide up, please. This analysis was conducted under the leadership of Teri Liegler at the UCSF clinical virology lab. It focused on the first 100 seroconverters in iPrEx, those that contributed to the primary analysis. A total of 96 of the first 100 could be tested, 35 in the active arm and 61 in the placebo arm.

The viral load, which is a critical parameter for assessment of the sampling or adequacy of sampling in minor variant assays, was comparable in the placebo and the active arm.

Next slide, please, or slide up. There were only two cases of minor variant drug resistance that were detected, one K65R and one M184V. Both of these cases of resistance detectable only with a minor variant assay were detected in the placebo arm. So there was no additional minor variant drug-resistant variance detected in the active arm.

Next slide. We were able to analyze all five of the individuals who had drug detected at the time of seroconversion or shortly before or after. So these are the results from the five individuals who had drug detected in the active arm seroconverters. The level of drug is typically quite low.

But in the setting of this low level of drug exposure, we did not see any drug resistance detected using this very sensitive assay, having a lower limit of cutoff of less than .5 percent.

This is an assay which controls for underlying template variability, which we have learned can cause false positive results. So this particular assay has been validated for variable

templates. So no additional drug persistence detected.

DR. GIORDANO: Can someone comment on, in the iPrEx study, the average risk? We saw what the eligibility criteria were to get into the study. But the average behavioral risk for the participants who were entered, did you see how high risk this group was?

DR. GRANT: So we will see if we can find the slide on this. Yes? Slide up, please.

So the mean reported numbers of male sex partners in the prior 3 months prior to enrollment in iPrEx was 18, a comparable level in the active and placebo arms. Unprotected receptive anal intercourse in the previous 3 months was reported in 59 percent in the active arm and 60 percent in the problem arm.

No condom with a partner who's either HIV-positive or of unknown serostatus was reported in approximately 80 percent of the group. Forty-one percent reported some sort of transactional sexual activity; this could include exchange of shelter

and food in exchange for sex. STIs were present and used to qualify them for participation in iPrEx in approximately a third or less of the cohort.

So this was a cohort expressing reported risk for acquiring HIV.

DR. FEINBERG: Dr. Corbett, do you have any questions?

DR. CORBETT: I actually have two questions. The first is, there was mention in both iPrEx and Partners PrEP that there were some patients who had detectable tenofovir-specifically exposures but did not seroconvert. And then there were others, of course, that had -- sorry -- that did seroconvert. And then there were others that had low concentrations but in fact did not seroconvert.

So in other words, there were discrepancies between exposures and the outcome in a small number of patients. So my question is, were there characteristics or other risk factors identified of those patients that may predict that discrepancy?

DR. GRANT: In the iPrEx study, only 10 percent of the seroconverters had any detectable

drug at the time of seroconversion. We can bring the slide up. So actually 8 percent, or 4 out of 48, had drug detected, any drug detected, at the time of seroconversion.

When we look in the past at the previous visit for which specimens were available, we see that 22 percent of the seroconverters had any drug detected. But only 2 out of 46 had drug detected at both the seroconversion time point and the previous visit.

So I think detectable drug over the course of the window when infection probably occurred was extremely rare, only 4 percent. Can we show a slide of the relationship between the level of tenofovir diphosphate and the risk of HIV infection in iPrEx?

More recently, at the retrovirus meeting, Dr. Peter Anderson, our pharmacological colleague, presented information relating -- slide up, please -- relating the concentration of tenofovir diphosphate in viably cryopreserved peripheral blood mononuclear cells in the active arm, related

to the extent of HIV risk reduction.

The placebo incidence here is given in black, and in blue is the data from the active arm, in which we show an exponential regression, indicating the relationship between drug level in cells and the risk reduction in iPrEx.

You can see here that relatively low -- that the few HIV-infected cases were associated with very low levels of tenofovir diphosphate. And once concentrations exceeded about 25, which is commensurate with 4 to 7 doses per week, risk reduction was 96 to 99 percent, and that the few HIV-infected cases that we have had tenofovir diphosphate levels that were lower than what you would get with 4 pills per week.

So bottom line is the drug levels in those few that had detectable drug and became infected were low.

DR. BAETEN: In Partners PrEP, we have a relatively limited number of individuals who became infected in the active arms in the first place, and then even smaller who became infected and have drug

detectable. There are four individuals who have drug detected at repeated visits and who became infected in the two active arms. That number is too small to do analyses at this time to try to define if there are specific correlates that would define them.

Importantly, the drug testing in Partners PrEP is at month 1, 3, and then quarterly thereafter. So we do not know what degree of exposure there was at the time HIV infection occurred, simply at the time clinic visits were scheduled. And that will be the limitation.

As we continue on in the Partners PrEP study with everyone on study product, we will continue to measure drug level and its relationship to seroconversion.

DR. CORBETT: So that sort of leads to my follow-up question. In these continued trials and demonstration trials, knowing that there's likely -- and we've seen data that there's differences between plasma and genital tract exposures, is there thoughts to evaluate genital

tract exposures in these follow-up studies?

DR. BAETEN: I think that's an excellent question. In Partners PrEP, we have both. We have swab, and in a subset, biopsy samples that we will have from individuals on PrEP that have not been analyzed yet. But it's an excellent question.

DR. FEINBERG: Dr. Blower?

DR. BLOWER: Thank you. I have a question for Dr. Mellors, but it probably -- well, it actually is a question for Dr. Tim Hallett. So can I ask you to get Dr. Hallett on the phone again? Or does Dr. Mellors ask you to?

DR. MELLORS: I think I ask permission. So on one knee?

(Laughter.)

DR. FEINBERG: Yes.

DR. MELLORS: Dr. Hallett?

DR. HALLETT: Yes, I'm here.

DR. MELLORS: Question for you.

DR. BLOWER: Hi, Tim. This is Sally. I have a question about the HIV epidemic modeling for Washington that you've done.

Looking at the slides that John showed, it doesn't appear that you've got any resistance in here. So did you assume that everyone who goes on PrEP was uninfected and therefore that testing was perfect, and that everyone who became infected on the drug was immediately taken off the drug?

DR. HALLETT: Yes. It's a good question. So in this model, this particular model that Dr. Mellors has presented, we did not include any of those issues that you mention, resistance spreading, imperfect testing, and so on.

But in lots of other models that we and others have done, this has been investigated quite comprehensively. And we've come to conclusions which quantitatively and qualitatively support the argument that Dr. Mellors put forward in his presentation, that when the models do capture that division of people who are on PrEP between those who are fully adherent and those who are not very adherent, and that when you are fully adherent there is a very low chance of becoming infected, we see little emergent resistance due to PrEP,

especially in comparison with what you would expect would come from ART.

So it's a limitation of the model that Dr. Mellors presented, that we didn't include those factors in the DC projections. But in other investigations, we have reason to believe -- well, reason to support what Dr. Mellors said about resistance not being thoroughly a major factor in PrEP.

DR. BLOWER: But -- well, actually, but you haven't published any models with resistance in them, have you?

DR. HALLETT: Well -- am I still on?

DR. BLOWER: I'm sorry?

DR. HALLETT: You can still hear me? Okay. So no, it's true that I haven't. But we have recently collected a group of four different modeling groups, which we have, and we have asked them to give us systemically standardized results, which do look at the marginal increase in the number of people infected, with a resistance rate of the virus for future PrEP.

I don't know if that slide is in the backup set --

DR. MELLORS: Slide up, please.

DR. HALLETT: -- but all those four levels from those four different groups do support that point on the slide.

DR. MELLORS: This is what you're referring to, Tim?

DR. HALLETT: That's right. That's correct.

DR. BLOWER: Is one of those mine? Predictions?

DR. HALLETT: One of those has a lead author of Supervie, yes.

DR. BLOWER: I'm sorry?

DR. HALLETT: One of them has a lead author of Virginie Supervie.

DR. BLOWER: I didn't hear that. Hello?

DR. HALLETT: One of the -- am I still coming through?

DR. MELLORS: Yes.

DR. HALLETT: Yes. So you asked, Sally, if one of the models is yours. I think the short

answer is yes. The lead author of one of the models is Virginie Supervie.

DR. BLOWER: Yes. My post-doc.

DR. HALLETT: Yes.

DR. BLOWER: Okay. But that's not what we published as results. And none of those -- so two of those, I think, are mine, San Francisco and Botswana. Yes?

DR. HALLETT: Yes.

DR. BLOWER: And the other two haven't been published?

DR. HALLETT: One of them has been published. One of them hasn't been published.

DR. BLOWER: Sorry?

DR. HALLETT: Because these are -- these are new results. They come from models that have been published --

DR. BLOWER: Yes.

DR. HALLETT: -- but the results haven't been published.

DR. BLOWER: Yes. So these haven't been published or peer-reviewed. So only two of them?

DR. HALLETT: The models have been peer-reviewed, yes.

DR. BLOWER: Yes. But the results haven't.

DR. HALLETT: Right.

DR. BLOWER: So only two of them have been peer-reviewed?

DR. HALLETT: Correct.

DR. BLOWER: So those are the ones I published. Okay. I wanted to clarify that.

Also, in the model that you're presenting for Washington, the results presented are linear. And to me, that indicates that there's something wrong with the model because the results should be nonlinear. So can you explain why the results are linear in the projections that Dr. Mellors showed?

DR. HALLETT: Yes. This is slide 191-192. So essentially, it's because we are looking at coverage levels which remain reasonably low. They go to a maximum of 10 percent of the population. If we were to go to higher coverage levels or make other assumptions about PrEP being targeted to higher-risk groups, we would see a saturation

effect and more nonlinear effects.

So the superficial appearance of linearity on these particular slides is only because we're looking at a small part of parameter space. And I should say that when we designed the scenarios to present here, we actually did a lot of things to be conservative in our projections, so we weren't being seen to overestimate the impact of a PrEP intervention.

So, for instance, we kept the coverage low. We didn't say a program would effectively capture those at highest risk for a program. We didn't assume any correlations, as Dr. Grant has mentioned, between those at greatest risk also potentially having greatest adherence. And we didn't assume any additional synergies of a PrEP program with HIV testing, behavior change programs, and linkages to ART for those testing seropositive.

So we designed these projections to have a modest impact so we didn't overstate it. And that's in general why you're seeing a perception of linearity here.

DR. BLOWER: So what percentage of reduction in infections is it?

DR. HALLETT: So that should also be in a backup slide. It's on the order of about 7 or 8 percent; for the red, 70 percent good adherence scenarios.

DR. BLOWER: I'm sorry. I didn't hear that.

DR. MELLORS: Seven or 8 percent.

DR. BLOWER: Seven or 8 percent. Okay.

DR. HALLETT: There should be a backup slide.

DR. MELLORS: Here's the percent.

Can you show the 70 percent good adherers percentage on the Y axis, please? There we go. Slide up.

DR. BLOWER: Then one last question. Do you also then calculate how much the incidence was reduced due to treatment, and how big a reduction was that?

DR. HALLETT: So we could calculate that in the model. We have a facility to do that. We don't have a slide prepared on that, and I haven't

got a number at my fingertips that I could give you right now.

DR. BLOWER: But it probably is about the same or more, I would guess.

DR. HALLETT: So treatment initiation in this population tends to be quite late. Until recently, median CD4 cell count at point of diagnosis was only 150, which would mean the impact of treatment on reducing its incidence would have been quite modest.

There have recently, since 2008, been increases in the CD4 cell count at diagnosis, implying that people are coming for testing earlier, which means that the impact of ART could be greater. But I wouldn't, without having the scenarios at my fingertips, want to give you a quantitative estimate for the impact of ART in this model.

DR. BLOWER: So for the next 10 years. Sorry. Okay.

DR. FEINBERG: So we are now 30 minutes behind, and I think we need to take a badly-needed

15-minute break. We'll return to the clarifying questions after that.

Members of the panel, remember you're not supposed to discuss the matters at hand during the break.

(Whereupon, a brief recess was taken.)

DR. FEINBERG: For the folks at the back of the room milling around the door, we're going to get started.

In the interest of time, we're going to have a rearrangement of the schedule here. We're going to have Dr. Piper from the Division of AIDS talk to us about the VOICE trial, and then we're going to move to the FDA presentation. And then we will have clarifying questions after that, and the clarifying questions can include questions for the sponsor as well as for the FDA.

Let me clarify what a clarifying question is. A clarifying question is, you're asking about a matter of fact. Is this really .1 and not .01? We're trying to be pretty specific about it because when we discuss the questions the FDA has posed to

us, we will have time later in the day to ask a lot more of them or what if, what if, what if questions later on. Otherwise we are never going to get through this day.

Okay, Dr. Piper. Are you here and ready? There she is already. I'm sorry. Dr. Jeanna Piper, Division of AIDS.

NIH Presentation – Jeanna Piper

DR. PIPER: Thank you for this opportunity to provide an update on the VOICE trial.

The VOICE trial is more formally known as MTN-003, and it is a phase 2B safety and effectiveness study of tenofovir 1 percent gel and tenofovir disoproxil fumarate and emtricitabine/ tenofovir disoproxil fumarate for prevention of HIV in women.

The study design is a five-arm trial with three oral arms and two vaginal gel arms. One key point to note is that because the tenofovir and the Truvada could not be made to look alike, the women in the three oral arms were required to take tablets each day, one that was or appeared to be

tenofovir and one that was or appeared to be Truvada. The study was powered to compare the two active oral arms to the placebo arm, oral arm, and to compare the tenofovir gel to the placebo gel.

The status of the accrual in the VOICE study was completed in June of last year. The enrollment, final, was 5,029 women, so it's met the target of approximately 1,000 women in each arm. The screened-to-enrolled ratio overall was 2.4 to 1.

As you can see, about 20 percent of the women who were screened were found to be HIV-positive at the time of screening. Some of the sites did recruit from VCT centers or have other prescreening techniques, so this is not completely reflective of the prevalence in the population.

Characteristics of the women who were enrolled in the VOICE trial. There were a little over 4,000 women enrolled at 11 sites in South Africa. There were 322 women enrolled at one site in Uganda, and 630 women enrolled at three sites in Zimbabwe.

Some important characteristics of note. The women enrolled in South Africa were younger and less likely to be married. The women enrolled in Uganda were less likely to have completed secondary education, and less likely to have used condoms at their last sexual act, and were more likely to have had recent sex with a non-primary partner.

Primarily, VOICE is an ongoing study, so I was asked to provide an update on the current status. This has in great part been modulated by the DSMB meetings. There have been five DSMB meetings regarding the VOICE trial, two of which only safety and study conduct were reviewed, and two at which efficacy was -- I'm sorry, three at which efficacy was also reviewed, of which two are really the focus of today's subjects.

This is a direct quote from the DSMB summary from the September 16, 2011 DSMB meeting. At that point, the DSMB recommended that "the oral single drug arm of tenofovir be stopped because of futility, as there is now clear evidence that this arm is not better than the placebo arm. All study

1 participants should be informed of this finding,
2 and those in the tenofovir arm unblinded to their
3 study treatment and have all study products, both
4 active and placebo, discontinued as soon as
5 possible."
6 They acknowledged the team's plan to begin
7 rolloff as scheduled at the beginning of 2012, but
8 did request that the tenofovir arm be terminated as
9 soon as feasible. And they recommended at that
10 time that the other arms of the study continue in a
11 blinded fashion, and that, as I mentioned, the
12 women in all the oral arms took two tablets per
13 day, so they did recommend that the tenofovir
14 placebo be discontinued in the two remaining oral
15 arms as it was no longer needed to be blinded to
16 tenofovir in those arms.
17 So to summarize, the two gel arms were to
18 continue as planned. The oral tenofovir arm was to
19 unblind and discontinue as soon as possible due to
20 futility. And then the oral Truvada and placebo
21 arms were continue the Truvada or Truvada placebo
22 as planned, but to discontinue the tenofovir

placebo.

An update on the current status with regard to these DSMB recommendations are that as of a couple weeks ago, 97 percent of the women in the oral tenofovir arm have had a product use end visit, and 91 percent have had a termination visit. And if note, the termination visits were scheduled to occur approximately 8 weeks after the product use end visit.

Moving on to the November DSMB meeting, in that meeting data was reviewed through a September 30, 2011 data cutoff. At that point, the DSMB statement is that 92 of the 94 targeted events have occurred in the vaginal gel comparison. On the basis of this data, the HIV incidence rate is 6.1 percent per 100 person-years for the placebo gel arm, and 6.0 per 100 person-years for the tenofovir 1 percent gel arm.

Therefore, the DSMB recommends that the vaginal gel comparison be stopped according to the futility stopped guidelines specified in the protocol. Participants should be notified of this

outcome as soon as possible, and the study team should develop a plan to systemically close out the vaginal gel arms as soon as is feasible.

The DSMB recommended that the comparison between the oral Truvada and placebo arms continue, per protocol, and the DSMB also stated that they had no major concerns about safety, and that they had reviewed the SAEs and the pregnancy rates and had no major concerns about them.

So to summarize, the two gel arms were to systemically close out as soon as feasible, and the oral Truvada and oral placebo arms were to continue per protocol.

An update on the status of this recommendation is that as of April 26, 95 percent of the women in both of the gel arms have undergone their product use end visit, and approximately 86 percent of the women in the two gel arms have had their termination visit performed.

So the timeline for closure of the VOICE study and analysis of the data is that for the two remaining oral arms, the Truvada and oral placebo

arm, the scheduled study closure visits began on February 1st with product use end visits in those arms.

All of the participants in those arms will have a termination visit 8 weeks following the end of product use, as has been the case for all of the study subjects. And the target is for all of the remaining study visits to be completed by August 13th. And with that, we anticipate to be able to provide the results publicly in first quarter of 2013, as has always been the targeted timeline for release of the results from this study.

An update on the status of the two remaining arms. As of April 26, 60 percent of the women have undergone a product use end visit, and 14 percent have had a termination visit.

Also, I was asked to provide an update on the VOICE-B, which is the bone density sub-study of the VOICE protocol. This sub-study was performed at four sites, one in Uganda and three in Zimbabwe. At those sites, all of the women who were enrolled

into the oral arms were offered participation in the bone density sub-study.

The women who enrolled in that study underwent a DEXA scan for bone density, and we did lumbar spine and hip. And that was done at enrollment, every 6 months while on study product, and then we've extended follow-up to 6 and 12 months after stopping study product to see if there is any resolution of any decreases that might occur.

At these sites, 518 women enrolled into the bone density sub-study, which was 93 percent of the women who were randomized to the oral arms at those sites, which is quite good.

So the timeline for that information to be available. So the women in the tenofovir arm have begun their six-month post-product use scans at this point. The analysis of the bone density data through the product use end visits for VOICE, we anticipate that that will be available at the time of the primary results of VOICE being released in the first quarter of 2013.

The analysis of the additional bone density data obtained 6 and 12 months after the product use in VOICE should be available approximately a year later, so approximately first quarter of 2014.

Thank you.

DR. FEINBERG: Thank you very much, Dr. Piper.

We will move now to the FDA presentation, the first one by Dr. Peter Miele.

FDA Presentation – Peter Miele

DR. MIELE: All right. Thank you. I will be presenting the FDA review so far for Supplement 30 for NDA 21-752 for Truvada.

This is the agenda for the presentation, which will focus primarily on the iPrEx and Partners PrEP trials, and will begin with an efficacy review, including both prespecified and exploratory post hoc analysis, and move on to review of the safety, resistance, and behavioral issues identified in the review and that are pertinent to the indication.

To remind you again of the indication that's

being proposed in this supplement, it's pre-exposure prophylaxis to reduce the risk of sexually acquired HIV infection in adults.

As you've already heard today, several clinical trials evaluating oral PrEP for prevention of sexually transmitted HIV have been initiated or completed in different at-risk populations around the world. All of these trials have evaluated tenofovir, either alone or in combination with emtricitabine.

The FDA review for this supplement focused on the clinical trial data from iPrEx and Partners PrEP, for which the applicant has submitted full data sets and clinical study reports. In addition, FDA reviewed data sets from CDC study 4323 in U.S. MSM for support of safety information, as this trial was conducted in a U.S. population and included a large DEXA sub-study.

Top line summaries of the CDC TDF2 and FHI PrEP trials were also submitted and reviewed. And as you've heard, what data has been made available from FEM-PrEP and VOICE, either at recent meetings

or through press releases, were taken into account.

The efficacy is based on iPrEx and Partners PrEP, both of which are randomized, prospective, placebo-controlled trials with very similar designs. The major difference between the two is that iPrEx studied a high-risk MSM population and evaluated emtricitabine/tenofovir as PrEP, whereas Partners PrEP studied heterosexual individuals, both men and women, in HIV-serodiscordant relationships where the HIV-infected partner was not yet on ART therapy. Partners PrEP also evaluated tenofovir as well as emtricitabine/tenofovir as PrEP.

Both trials included monthly HIV testing as well as risk reduction counseling, provision of condoms, and treatment of any symptomatic sexually transmitted infections at every clinical visit. Both trials were also powered to show at least a 30 percent reduction in risk of HIV acquisition, a standard adopted from HIV vaccine and microbicide clinical trials.

You've already heard about the definition

of high risk for MSM in iPrEx from Dr. Grant in response to a committee question, so I'll move on.

About 2500 MSM were involved in iPrEx, with equal distribution between the arms. Baseline demographics were also comparable between the two arms. Median duration of exposure was 77 weeks. By end of treatment, there were 83 HIV seroconversions in the placebo arm and 48 in the emtricitabine/ tenofovir arm, for a relative risk reduction of 42 percent by Cox regression, with a 95 percent confidence interval of 18 and 60 percent.

FDA also conducted a sensitivity analysis in iPrEx that treated all subjects who utilized post-exposure prophylaxis, or PEP, of which there weren't many, as HIV seroconverters, and found that the use of PEP in this trial did not statistically affect the overall efficacy results.

In iPrEx, we found that high self-reported adherence was not reliable as it correlated poorly with detectable drug levels. On the other hand, poor self-reported adherence was predictive of

undetectable drug concentrations.

In a sub-study of intracellular drug concentration in HIV seroconversion, the estimated risk reduction among subjects with measurable drug concentrations was 87.5 as compared with placebo. In the next few slides, I will demonstrate how FDA determined this. But first let me briefly review some basic tenets of tenofovir pharmacokinetics as they relate to this subgroup analysis.

As we know, the half-life of tenofovir, and emtricitabine, for that point, is much longer in peripheral mononuclear blood cells, or PBMCs, than it is in plasma. PBMC or intracellular drug concentrations, therefore, are more reflective of long-term drug adherence. The FDA PK subgroup analyses focused only on intracellular drug concentrations of tenofovir.

The objective here was to evaluate is intracellular concentrations of tenofovir in PBMCs correlated with protection from HIV infection. PBMCs were collected from all subjects at baseline, every 24 weeks, and at end of trial or

seroconversion. The FDA analysis used PK measurement from the study visit retrospectively determined to be closest to the time of HIV infection.

For cases, all 48 HIV seroconverters from the emtricitabine/tenofovir arm were used. And as controls, three uninfected subjects from the same arm were matched to each seroconverter, for a total of 133, after the removal of 11 subjects who served as controls twice. All three controls were matched by site and time on treatment, and one control was also selected based on positive URAI status at screening.

The results show that a lower proportion of seroconverters -- 8 percent -- had measurable intracellular tenofovir concentrations relative to their matched HIV uninfected controls at 38 percent. The FDA findings at this point are consistent with those reported by the iPrEx team for this case control sub-study.

One limitation of the sponsor's subsequent analysis based on these data is that the sponsor's

method only provided the relative risk reduction between the measurable and nonmeasurable subjects within the tenofovir/emtricitabine arm. It did not provide absolute event rates, as based on measurable intracellular drug concentrations, so that comparisons to placebo cannot be made.

FDA therefore conducted an exploratory efficacy analysis by extrapolating the findings from this case control sub-study to the entire emtricitabine/tenofovir-treated population in order to estimate the relative risk reduction as compared with placebo and as based on measurable intracellular drug concentrations.

In order to do this, an assumption was made that the proportions of subjects with measurable and nonmeasurable drug concentrations were consistent between the control group and the entire emtricitabine/tenofovir arm. To illustrate how this was done, allow me to demonstrate a simple exercise.

Say we wish to know in a population of 1,000 how many individuals are male and how many

are female. We can randomly select a subset of 100. In that subset, say we find that 50 are men and 50 are women. We can then extrapolate this ratio of men to women from the subset to the entire population of 1,000 and assume that 500 are men and 500 are women in our population.

With that, I will now walk you through the assumptions made for the exploratory efficacy analysis in iPrEx.

In the emtricitabine/tenofovir arm, a total of 1224 subjects were followed. We know 48 of these subjects had an HIV seroconversion event during treatment, leaving 1176 uninfected subjects in the arm. From the previous analysis, we know that 44 of the HIV seroconverters had nonmeasurable intracellular tenofovir concentrations, and 4 had measurable concentrations.

From the HIV uninfected group, we have PK data from 133 control subjects, which will serve as our subset. And again, from the previous analysis, we know that 62 percent of them had nonmeasurable intracellular concentrations, and 38 percent had

measurable concentrations.

We then extrapolated this ratio of 62 to 38 percent to the entire uninfected cohort of 1176 in the emtricitabine/tenofovir arm. Based on this extrapolation, it was assumed that 451 HIV-uninfected subjects treated with emtricitabine/tenofovir were likely to have had measurable intracellular concentrations, and were thus adherent to medication, whereas 725 were likely to have had nonmeasurable concentrations. After adding back the HIV-infected subjects, we calculated the event rate per subject for the entire FTC/TDF arm.

Now, before I go further, I want to emphasize that this is an assumption, that the proportion of subjects with measurable and nonmeasurable drug concentrations was constant for the entire HIV-uninfected group in the treatment arm. However, we know that control subjects in the case control sub-study were not randomly chosen, but instead were selected to match the HIV-infected cases.

In order to test the validity of the assumption, FDA conducted several sensitivity analyses that showed no significant impact on the overall results when matching covariates and other factors affecting adherence were taken into account.

Moving on, using the event rates per subject, absolute seroconversion rates per person-year were calculated for the entire emtricitabine/tenofovir arm based on the measurable intracellular drug concentrations, as shown on the left. The seroconversion rate for subjects with nonmeasurable drug concentrations was estimated at 3.6 per 100 person-years, which is not significantly different than the observed 4.2 percent rate in the placebo group.

For subjects with measurable intracellular drug concentrations, the seroconversion event rate was estimated at less than 1 in 100 person-years, substantially lower than either the placebo or nonmeasurable groups.

Translating the estimated absolute

seroconversion rates into relative risk reduction as compared to placebo, and shown here on the right, FDA found that subjects with nonmeasurable tenofovir concentrations had limited additional protection from HIV infection compared with placebo. However, the relative risk reduction in subjects with measurable intracellular drug contains was estimated at 87.5 percent.

These results suggest that increased medication adherence, as determined by measurable intracellular tenofovir concentrations, reduce the risk of acquiring HIV infection, while poor adherence to taking drug was not significantly different than taking placebo.

This slide shows the results if we further break the measurable group into low and high measurable drug concentrations, based on the median intracellular tenofovir concentration of 15.6 femtomoles per million cells.

When this is done, the risk reduction, as shown on the right, is about 76 in the low measurable group but about 100 percent for the high

measurable group. Please note, though, that these are point estimates with associated uncertainties. Nonetheless, the point to be made here is that better adherence, as determined by intracellular tenofovir concentrations, is associated with greater efficacy.

In summary, despite the different approaches used, the FDA findings were similar to those reported by the iPrEx team.

Going further, using the PK data from the case control subgroup, FDA conducted exploratory analyses to identify baseline characteristics that might have correlated with better adherence, again as determined by measurable intracellular tenofovir concentrations. Age, education, and the reporting of unprotected anal sex at screening were found to correlate with better adherence.

This fourth figure shows the proportion of subjects with measurable intracellular drug concentrations if the three baseline characteristics are combined. Since these adherence correlates were identified using the

relatively small cohort of 133 HIV-uninfected subjects, FDA conducted subgroup efficacy analyses in the entire iPrEx population to see whether these same baseline characteristics also correlated with greater risk reduction.

This slide shows a subgroup efficacy analysis based on the previously identified subject characteristics. And again, I want to point out that these results here represent the entire iPrEx population.

FDA found that subgroups with the baseline subject characteristics that were correlated with better adherence -- name, age, education, and URAI at screening -- also demonstrated greater risk reduction relative to placebo as compared to the subgroups without the characteristics.

Based on the differences observed in HIV incidence between the emtricitabine/tenofovir and placebo arms within each of these subgroups, it appears that the overall risk reduction seen with emtricitabine/tenofovir is most likely related to drug adherence and not to some other factors, such

as differential condom usage between the subgroups with identified characteristics and the placebo group as a whole.

An additional point worth highlighting here that has been mentioned before is that subjects with no URAI reported at screening had low event rates in the placebo arm, which likely contributed to the inability of the trial to show a beneficial risk reduction in this subgroup.

Moving on to the Partners PrEP trial, the trial investigators have already reported the relative risk reductions observed with tenofovir and emtricitabine/tenofovir as compared with placebo. FDA's review of the data yielded the same overall efficacy results as presented by the sponsors.

In this slide, the efficacy outcomes are broken down by gender. And as can be seen here, the incidence of HIV seroconversion was higher for women than men in the placebo arm, which is consistent with observational data that indicate that women are at greater risk of acquiring HIV

infection than men in this population.

Nonetheless, both tenofovir and emtricitabine/tenofovir significantly reduced the risk of HIV infection in both men and women compared with placebo. There was no statistical difference in the risk reduction between men and women for either tenofovir or emtricitabine/tenofovir.

FDA further conducted sensitivity analysis to evaluate the impact of the initiation of ART in the HIV-infected index partner, as well as to treatment interruptions of women who became pregnant or were breast-feeding, and found that these events had no impact on the overall efficacy results.

A post hoc case cohort analysis was also conducted within Partners PrEP to evaluate the relationship between tenofovir exposures and protection from HIV infection. In Partners PrEP, only plasma samples were collected. The FDA analysis focused on the emtricitabine/tenofovir arm.

Adherence in this analysis was categorized by always-, sometimes-, and never-measurable plasma concentrations over multiple time points. As can be seen here in green on the right, the HIV-uninfected cohort had a much higher percentage of always-measurable plasma concentrations than the HIV-infected cases, again indicating better adherence in this cohort.

As was done with iPrEx, FDA conducted an exploratory analysis to quantify the exposure/efficacy relationship in Partners PrEP. The same assumptions and extrapolation methods previously described were used for this analysis.

FDA found that by extrapolating the PK findings from the case cohort sub-study to the entire emtricitabine/tenofovir arm, the estimated seroconversion rate in the group of subjects who always had measurable plasma concentrations was 0.1 percent, which translated to a risk reduction of 94 percent relative to placebo.

Importantly, these findings were consistent with what was shown for iPrEx. Therefore, to

summarize, based on exploratory PK analyses from two independent trials, it appears that better adherence correlates with greater risk reduction.

I'll now move on to the safety portion of the presentation, focusing on renal and bone issues related to tenofovir.

Tenofovir is predominately renally excreted, both through glomerular filtration and active tubule secretion. The site of tenofovir-induced kidney dysfunction is thought to be the proximal renal tubule cell. Tenofovir is transported from systemic circulation, shown here on the bottom, into the proximal renal tubule cell by O transporters and secreted into the tubule lumen by MRP transporters.

These transporters may play a role in the development of renal dysfunction when tenofovir is co-administered with drugs that either enhance entry of tenofovir into the renal tubule cell or inhibit MRP excretion of tenofovir into the lumen.

As an example, ritonavir is thought to interact with MRP transporters and inhibit the

excretion of tenofovir, which may explain the increased risk of tenofovir-related nephrotoxicity when co-administered with boosted protease inhibitors.

Some of the bone adverse events associated with tenofovir may also be related to proximal tubule dysfunction. Vitamin D is activated into calcitriol in the mitochondria of proximal tubule cells, shown here in purple, and decreased activation of vitamin D may lead to increased levels of parathyroid hormone and a decrease in bone mineral density.

As just described, renal adverse events associated with tenofovir are thought largely to arise from proximal tubular dysfunction, and this may be clinically unapparent and occur prior to any decline in renal function.

Severe cases, which may be infrequent, may manifest as a partial or complete Fanconi syndrome, with or without reduction in creatinine clearance. Proximal tubulopathy may also lead to decreased bone mass or osteomalacia due to phosphate wasting

or decreased activation of vitamin D.

The following list includes laboratory abnormalities that may precede or accompany a reduction in creatinine clearance, and include increased fractional excretion of urinary phosphate or uric acid; proteinuria; non-diabetic glycosuria; elevations in serum creatinine and metabolic acidosis; and decreased activation of vitamin D, with a corresponding increase in parathyroid hormone.

Through HIV clinical experience, the following risk factors have been identified for tenofovir-associated renal adverse events. Low CD4 count and advanced HIV disease are specific to HIV infection, but the remaining factors may be relevant to HIV-noninfected individuals, which leads us to the safety findings from the clinical trials of PrEP.

FDA review of safety iPrEx and Partners PrEP did not reveal any new adverse events. The rates of serious or severe adverse events were low and balanced between the active and placebo arms in

both trials. In general, emtricitabine/tenofovir was well-tolerated, with few discontinuations for tenofovir-related adverse events. However, adherence in iPrEx should be taken into account when assessing the safety findings from that trial.

In iPrEx, seven subjects interrupted emtricitabine/tenofovir for creatinine elevations, versus three placebo subjects. Six of these subjects, we found, resumed emtricitabine/tenofovir without further incident. In Partners PrEP, four subjects permanently discontinued tenofovir or emtricitabine/ tenofovir for creatinine clearance decreases below 50 versus one in placebo subject. Creatinine clearance returned above 50 with removal of the study drug.

An additional subject in Partners PrEP discontinued tenofovir for a grade 1 creatinine increase, which by the protocol was defined as an increase 1.5 times the baseline serum creatinine. In creatinine, this subject was still elevated at the time of exit from the trial.

This slide shows the creatinine clearance

changes for the four subjects in Partners PrEP who permanently discontinued tenofovir or emtricitabine/ tenofovir. All four cases occurred in women. And as you can see, all had estimated creatinine clearances in the 60 to 70 range at baseline.

The low creatinine clearance that prompted discontinuation was observed at a single time point, shown by the red arrows. It improved promptly with removal of the study drug. No proteinuria or glycosuria was associated with any of these events.

The incidence of graded increases in serum creatinine or reductions in serum phosphorus were generally comparable between the tenofovir-containing arms and the placebo arms across the three trials evaluated, including the CDC 4323 phase 2 safety trial in U.S. MSM. Note that iPrEx and Partners PrEP both used different variations on the DAIDS Toxicity Grading Table for grading laboratory abnormalities. In order to make cross-trial comparisons between the two, the results

shown here are using the applicant's grading scheme.

Review of urinalysis data from iPrEx and Partners PrEP showed no significant differences between the active and placebo arms in terms of recurrent proteinuria or proteinuria accompanied by glycosuria or increased creatinine. Most findings of proteinuria or glycosuria were isolated and were either trace or 1-plus on urine dipstick.

In iPrEx, the one subject who permanently discontinued emtricitabine/tenofovir due to a grade 1 increase in creatinine also had evidence of trace proteinuria on more than one occasion. The proteinuria and increased creatinine persisted for a period of time after discontinuation of emtricitabine/tenofovir.

Also, in iPrEx, five of the six emtricitabine/tenofovir subjects with concurrent proteinuria and glycosuria also had evidence of graded hypophosphatemia during follow-up. In these cases, the urine abnormalities were either trace or 1-plus and typically preceded or were reported

concurrently with the graded hypophosphatemia.

In addition, two of these five subjects also had evidence of bone mineral density loss greater than 5 percent from baseline on DEXA scans obtained during treatment or post treatment.

Similar to other trials conducted with tenofovir, mean changes in creatinine clearance over time were minor and not significantly different compared with placebo in these trials. This slide shows the mean change in creatinine clearance from baseline through week 96 in iPrEx, and similar findings were observed in Partners PrEP.

Because clinicians sometimes observe small increases in serum creatinine with tenofovir use that do not appear to resolve and do not meet criteria for a graded elevation in a clinical trial, FDA conducted a categorical analysis of creatinine increases in the three submitted trials using as a cutoff a 20 percent increase from baseline observed on more than two visits or two consecutive visits, not including confirmatory

visits. Mean subject age was similar between the treatment and placebo arms in each trial.

What we found was a very small but consistent imbalance across the three trials between the tenofovir-containing arms and the placebo arms. The difference between the two was greater in the CDC 4323 and Partners PrEP trials than in iPrEx. Mean increases of 20 percent from baseline were also observed at one year in both of these trials, and the lower increase in iPrEx may reflect the lower adherence to study drug in that trial.

Where urinalysis data were available, no correlation between increased serum creatinine and the incidence of proteinuria or glycosuria was found. Also, mean serum phosphorus values did not change significantly compared to baseline in this cohort.

Since small changes in serum creatinine have been consistently observed in clinical trials of tenofovir, FDA looked for any correlation between changes in serum creatinine and changes in

laboratory values associated with bone turnover or changes in bone mineral density on DEXA scan.

FDA validated DEXA scan data from CDC 4323, and this was chosen for the analysis because adherence to study drug was estimated to be about 80 percent based on the use of MEMS caps and because the trial was conducted in a U.S. population.

Interestingly, low bone mineral density, defined as a Z-score less than or equal to negative 2, was observed more frequently than expected in the enrolled MSM population, with a median age of 41.

Baseline demographic factors that correlated with low bone mineral density included the use of amphetamines and the use of inhalants. An inverse correlation was found with intake of vitamin D or multivitamins. Sixteen of the 20 subjects with low baseline bone mineral density were further evaluated, and two were found to have vitamin D deficiency and one with hypogonadism.

To conduct the categorical analysis BMD

changes, cutoffs of greater than 3 percent and greater than 5 percent decrease from baseline were used. The 3 percent cutoff was chosen because a greater-than-3-percent decrease in bone mineral density is more than what would be expected in healthy men. The 5 percent cutoff is derived from clinical observations of BMD loss in postmenopausal women over a 2-year period.

In CDC 4323, at month 24 or the end of treatment, a greater proportion of subjects had lost greater than 3 percent of bone mineral density in the tenofovir group compared with subjects in the placebo group at both the total hip and lumbar spine, although reductions were more pronounced in the hip.

Getting back to our categorical analysis of creatinine changes, FDA looked at the incidence of elevated alkaline phosphatase associated with increased creatinine and found that about half of the subjects with creatinine increases also had an increase in alkaline phosphatase. However, similar elevations were found in subjects without

elevations in creatinine.

Nonetheless, among subjects with increased creatinine who participated in the DEXA sub-study, there was a twofold difference between the tenofovir and placebo arms in the percentage of subjects with bone mineral density loss greater than 3 percent. This difference was in contrast to subjects without creatinine increases, shown on the bottom, where the percentages were 57 versus 45 percent for the tenofovir and placebo arms respectively.

For all subjects with bone mineral density loss with or without creatinine increase, alkaline phosphatase elevations were seen more frequently in the tenofovir arm than in placebo. There was no difference between the arms in terms of use of concomitant medications such as NSAIDs or acyclovir.

I would like to emphasize that this is an exploratory analysis based on a very small number of subjects. The strength of an association or any clinical relevance is therefore not known.

Moreover, this finding was not observed in iPrEx, as elevations of alkaline phosphatase were observed in less than 5 percent of subjects. This may be related to the younger mean age of participants in that trial or due to other factors.

Because new onset back pain was reported twice as often in tenofovir subjects compared to placebo subjects in CDC 4323, a close review of subject data was conducted looking for any correlation between this clinical event and laboratory or bone mineral density data.

We found no differences in terms of mean change in serum creatinine, serum phosphorus, or alkaline phosphatase from baseline to end of treatment. Among the small number of subjects with back pain and bone mineral density loss, the proportions were greater in the placebo arm.

FDA also looked at other adverse events in the musculoskeletal and connective tissue system organ class such as arthralgias and myalgias and found no imbalance between the tenofovir and placebo arms.

Slightly more subjects receiving tenofovir experienced bone fractures as compared with placebo in CDC 4323. However, the clinical relevance of this difference is unclear, given the small numbers. Some of the fractures appeared to be trauma-related, but none were considered drug-related. And as you've heard, other PrEP trials with tenofovir have not shown a significant difference in fracture rates between active and placebo arms.

To summarize, no serious events related to tenofovir were observed in about 4500 individuals who received either tenofovir or emtricitabine/tenofovir in two large clinical trials and one small supportive safety trial. Very few subjects, about six, discontinued tenofovir or emtricitabine/tenofovir for decreases in creatinine clearance or increased creatinine, and a return to baseline was documented in five of these six.

A small but consistent increase in incidence of serum creatinine elevation relative to placebo was observed across the clinical trials, consistent

with previous trials. But this did not appear to correlate with increased risk of clinical events or other laboratory abnormalities.

Also, a small but significant reduction in bone mineral density relative to placebo was observed with tenofovir or emtricitabine/tenofovir in two trials of MSM.

Because the long-term significance of bone mineral density reductions are unknown at this time, consideration should be given to identifying and managing causes of osteoporosis and osteomalacia. This may also assist in identifying individuals for whom baseline and follow-up DEXA scans may be useful and for whom vitamin D and calcium supplementation might be a consideration.

I'll move on now to resistance issues. This slide summarizes the NRTI-associated resistance, as observed among subjects randomized to the active arms of the iPrEx and Partners PrEP trials, as well as the CDC TDF2 trial in Botswana. Infections that occurred on placebo are not included in this slide.

In parentheses below the number of

infections are the resistance mutations identified within each group. No resistance was identified among subjects who became infected during the treatment phase of their respective trials, which may be consistent with poor adherence among those who failed PrEP.

In contrast, several cases of resistance -- 6 out of 11 -- were found among subjects who had been enrolled in the trials with unrecognized HIV infection and who subsequently received either tenofovir or emtricitabine/tenofovir.

These genotypic data are from isolates collected at least one month into the treatment phase. The asterisks identify those cases where wild-type virus was confirmed in pretreatment samples, thus likely representing the emergence of resistance due to selection by the drugs. The other two cases may represent transmitted resistance.

Moving on to behavioral changes, risk compensation was not evident in either the iPrEx or Partners PrEP trial. The percentages of subjects

reporting unprotected sex, rectal in iPrEx and vaginal in Partners, decreased from baseline during the course of the trials.

Since self-reported condom use is a subjective measure, FDA also reviewed rates of sexually transmitted infections over time as an objective measure of sexual behavioral changes. This slide shows the baseline prevalence of any STI in the iPrEx population and the post-baseline incidence, and as you can see, STI rates decreased in both the emtricitabine/tenofovir arm and the placebo arm. Likewise, STI rates decreased from baseline during follow-up in Partners PrEP.

To conclude, FDA found the safety and efficacy of emtricitabine/tenofovir for the prevention of HIV infection in high-risk individuals is supported by two large clinical trials. Regular HIV testing, adherence, and behavioral counseling on safer sex practices, including condom use, are essential components of healthcare delivery around PrEP, and were key components of the clinical trials that evaluated

oral PrEP.

Risk compensation was not observed in these clinical trials, and resistance was identified only in individuals who took tenofovir or emtricitabine/tenofovir during early infection prior to their diagnosis of HIV. Careful assessment of risk factors for HIV infection should be undertaken and can identify individuals for whom PrEP may be appropriate.

I'll conclude there and turn the podium over to Dr. Carolyn Yancey for review of the REMS strategies.

FDA Presentation – Carolyn Yancey

DR. YANCEY: I believe I stand between you and lunch, so I will proceed. I'm going to talk about the proposed risk evaluation and mitigation strategy for Truvada for a pre-exposure prophylaxis indication.

The agenda includes a background about risk evaluation and mitigation strategy. I'll discuss the elements, if you will, and details that are currently proposed for this REMS, as we use it in

terms of an acronym. And then I will close with two slides that will present some of the challenges from the FDA's perspective.

In terms of the background, the name of the law that Congress passed September 2007 is the Food and Drug Administration Amendments Act. In the FDA, we have lots of acronyms, and this acronym is pronounced FDAAA. It actually amends the Federal Food, Drug & Cosmetic Act, which was passed in 1938. So here we are, 69 years later, and the agency has been authorized to require submission of a risk evaluation and mitigation strategy.

This particular strategy can be implemented pre-approval or it can be implemented post-approval. Post-approval would occur if the agency becomes aware of new safety information and determines that such a strategy is necessary to ensure that the benefits of that drug will outweigh the risks.

There are six factors that are written into the law, FDAAA, that are considered when we look to weigh whether or not a REMS would be required:

estimated size of the population likely to use the product; the seriousness of the disease or condition that's to be treated with the product; expected benefit of the product with respect to the disease or condition; expected or actual duration of treatment of the product; seriousness of any known or potential adverse events that may be related to the product; and the background incidence of those key events in that population that are most likely to be using the product; also, whether or not that product is a new molecular entity.

I'm going to walk through in the next four slides the elements of a REMS. In terms of the way a REMS is structured, there are overarching goals for any REMS that's required by the agency. Those goals are based on the serious risks that have been reported in the clinical development program, risks that are serious to the extent that the agency believes there are other risk mitigation strategies that should be put in place before it would be introduced into the public use.

A medication guide is FDA's patient-friendly labeling. It can be required as part of labeling if the agency determines any of the following. Labeling could help a patient avoid a serious adverse event or help prevent that event. The product has serious risks that could affect a patient's decision to use that product, or even to continue to use that product. Patient adherence to directions would be crucial to the effectiveness has been demonstrated in the clinical development program.

I can't underscore enough that a medication guide can be required in the labeling. It need not be required in a REMS. So there are two different pathways the agency can take with this patient-friendly labeling, if you will.

A communication plan is an additional element that can be included in a REMS. The communication plan includes FDA-approved materials that are used to support the implementation of a REMS and/or to inform the healthcare providers about the serious risks with the product.

A third category in terms of elements that can be placed in a REMS program is entitled Elements to Assure Safe Use. Again, we have many acronyms. This acronym is pronounced ETASU.

To mitigate a serious risk in the labeling may require one or more of these six elements to assure safe use. I want you to focus your attention on the first one, A. This is in regard to healthcare providers who prescribe the drug, have particular training or experience or are specially certified. This particular element, as I'll discuss shortly, is the one element to assure safe use, ETASU, that is proposed in the REMS for Truvada.

The other options, as you see them, can address pharmacies, practitioners, healthcare settings like a hospital where a product is to be dispensed. It may only be dispensed to certain patients, again in a special setting. There may be a requirement for a laboratory test, documentation of safe use, even a patient registry.

There's another element that's not included

in the slides, and I didn't include it since it's not in the proposed REMS for this product, and that is an implementation system. Implementation systems are additional measures that an applicant/sponsor, if you will, would need to be taking to monitor the implementation and make sure that it's done correctly. Again, that's not a part of the proposed REMS for this product today.

Elements to assure safe use are not mutually exclusive. I can't emphasize that enough. There is considerable overlap in the way in which elements can be implemented in a single program. Some elements to assure safe use include restrictions to drug distribution, and that would be based on the way the drug is prescribed by the prescriber, or the way it might be dispensed. Again, it could be a hospital setting. Educational materials are important components of each of those ETASUs.

The last component which is an element of a REMS and required is a timetable for submission of assessments. Every REMS for a new drug

application, NDA, or a biologic license application, BLA, must have a timetable for submission of assessments of the REMS.

Now, uniquely, a timetable for submission of assessments is not included in an abbreviated ANDA -- again, an acronym, A-N-D-A. This timetable may vary, but it would be no less than 18 months, 3 years, and 7 years. But I underscore it may vary. REMS can be required to have additional assessments, depending on what is demonstrated in that postmarketing safety program. And also, a remained could, in fact, be eliminated after 3 years that it's been in place and assessed.

So what are the risks for mitigation with Truvada for a PrEP indication for prevention of HIV? We've certainly heard comprehensive and excellent presentations this morning about the efficacy and the safety of this proposed product.

From the agency's perspective, we believe that the major risk for mitigation in a REMS program is the development of drug resistance. I can't underscore that Truvada, as you've heard, may

not prevent HIV infection. Drug-resistant variants may develop in persons continuing to take Truvada for a PrEP indication who converted from a negative serostatus to a positive serostatus.

We also considered education. And education, as you will see in a few additional slides, is a major effort of this risk mitigation strategy. But education, we believe, needs to focus on two things, certainly, you've heard much about this earlier today, adherence and screening: adherence to checking the HIV serostatus prior to initiating Truvada for a PrEP indication; monitoring the status throughout chronic administration of Truvada for a PrEP indication; taking a once-daily oral dosage regimen; and, of course, practicing safer sex; again, as discussed earlier, screening for sexually transmitted infections prior to and throughout administration of Truvada for PrEP; and of course, screening for signs and symptoms of acute HIV infection, again, prior to and throughout administration of this product for this indication.

The educational materials in the public domain were considered. These two you've heard mentioned earlier, "Guidelines for Use of Antiretroviral Agents," and "HIV-1 Infected Adults and Adolescents," recently revised March 2012, and, of course, the "CDC Interim Guidance on HIV Pre-Exposure Prophylaxis in Men Who Have Sex with Men." And that was February 2011.

We also clearly listen to stakeholder feedback. This was mainly gathered from the Forum for Collaborative HIV Research, which was held August 2011. This included diverse stakeholders in that audience, academicians, federal and state government, industry, public/private interest groups, as well as public health officials.

What the agency heard was that stakeholders do not agree with a restricted drug distribution program, mandatory or voluntary registry, or the prescribers of this proposed product, or the persons who would be taking Truvada for a PrEP indication. Stakeholders further did not agree with documentation of safe use conditions prior to

dispensing. That would be, in this case, a negative HIV test prior to receiving a prescription.

Stakeholders agreed that a restricted risk mitigation program could be circumvented, as mentioned earlier, because Truvada is approved and is marketed in the United States. Education should be considered in the context of existing preventive initiatives in the public domain, and certainly that scope is broad, as you've also heard earlier today. Stakeholders also expressed a desire that postmarketing surveillance should monitor drug-resistant variants, and of course to the extent possible.

So let's now talk about the proposed REMS for Truvada for a PrEP indication. The next six slides will walk you through what is currently being proposed. This looks like an outline, and that's very much what those documents look like that we call a REMS.

Number one are the goals. Number two, the REMS elements. In this proposed REMS, we have

three elements: a medication guide, prescriber training and education, underscore not linked to restricted drug distribution or access, and a timetable for submission of assessments.

The goals. These are the proposed goals, as you see them on this slide. And they would be to inform and educate prescribers, other healthcare professionals, and individuals at high risk of acquiring HIV infection about the importance of strict adherence to the recommended dosing regimen; the importance of regular monitoring of HIV-1 serostatus to avoid continuing to take Truvada if seroconversion has occurred to reduce the risk of development of resistant HIV-1 variants; also, to communicate the fact that Truvada for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV infection, and that other preventive measures should also be used.

Medication guide. The agency is proposing that a medication guide be required in this proposed REMS. This would be a Truvada medication

guide that is for the moiety. It would be dispensed with each prescription.

If this indication were to be approved, then there would be two indications that would be captured in the information of this medication guide: the existing approval, education of patients with established HIV infection; the proposed approval would be for the education of uninfected individuals taking Truvada, and those risks have been articulated earlier.

We are proposing one element to assure safe use in ETASU: Specifically, prescriber training and education, again, not linked to restricted drug distribution. The target prescribers that are proposed are primary care physicians, including internal medicine, family practice, and general medicine; infectious disease specialists; emergency medicine physicians; obstetricians; gynecologists, and addiction specialists.

Prescriber training. We have two major components for prescriber training that are being proposed. Number one is dissemination of safety

risk information to relevant professional organizations for outreach to prescribers likely to prescribe Truvada for a PrEP indication for prevention of HIV infection.

The second area under this broad training and education program would be the educational materials. They are proposed as a "Dear Healthcare Provider" letter; educational materials to prescribers; a training guide for health care providers; a provider safety brochure as well as an individual safety brochure, and this will focus on important safety information about Truvada for a PrEP indication; the wallet card, as was clarified earlier, is directed to uninfected individuals; and there will be a REMS-specific website.

The materials under the training and education ETASU are materials that we believe are best given to an uninfected individual by way of their prescriber, though you see materials here, the wallet card, for example, that is directed at the individual user.

Timetable for submission of assessments:

Periodic REMS assessments will be submitted to the FDA according to a specified timetable. The proposed assessments will be at 6 months, 12 months, and annually thereafter.

A restricted distribution plan. I mentioned it earlier. We listened to stakeholder feedback last August. And we certainly waited internally in a very robust way. The agency recommends that a restricted distribution plan not be part of the Truvada REMS, and it was for two major reasons. We felt that this could adversely affect access for patients with established HIV infection being treated with Truvada. We also felt that any restrictions in terms of distribution could adversely create barriers to access for uninfected individuals taking Truvada for a PrEP indication for prevention of HIV infection.

The REMS assessment, as it currently is proposed, includes three broad categories. The first is surveys. There are proposed surveys for prescribers, and there are proposed surveys for uninfected individuals. These surveys look to

gather information about the understanding of key safety risk messages in the educational materials.

The second category of the REMS assessment as it currently is proposed are the number of prescribers who complete the training and education program as has been presented. The applicant proposes to maintain a database of prescribers who complete this training and education program.

Drug use data for Truvada for a PrEP indication, we are looking to capture Truvada prescriptions without concomitant antiretroviral products, the assumption being that if we can capture through pharmacy/vendor data these prescriptions without other concomitant antiretrovirals, we are most likely to capture Truvada for the proposed indication of pre-exposure prophylaxis.

We also want to look at the number and type of prescribers by specialty who prescribed Truvada without concomitant antiretroviral products. And of course, we will have to consider in that data that Truvada certainly can be prescribed without

concomitant antiretrovirals in post-exposure emergency situations, if you will.

So a REMS assessment plan will be based on information submitted to the agency. And that will be assessments, and then we'll conclude of whether or not the REMS is meeting its goals and whether or not a modification is needed to the REMS. With the submission of any assessment, modifications can be required by the agency to the sponsor.

In the last two slides, I'll conclude with just articulating some of the challenges that we see with the REMS assessment plan. We believe it'll be challenging to determine if the REMS impacts reducing the number of individuals continuing to take Truvada for a PrEP indication who converted from HIV-negative to HIV-positive. We also believe it will be challenging to understand whether or not the REMS impacts reducing the development of drug-resistant HIV variants in individuals who would be taking Truvada for a PrEP indication.

We recognize, again, though we will be using

pharmacy-vended data, and I articulated the approach to capture data for this proposed indication, that the number of individuals taking Truvada for a PrEP indication for prevention of HIV will still be very challenging to capture; and again, recognizing that a singular prescription reported in a database for Truvada without concomitant antiretrovirals could have been prescribed for post-exposure to HIV infection.

There are three more items that I wanted to share with you in closing in terms of challenges for this REMS assessment plan. As you recall from the items in the REMS, there are no registries in this REMS program. There are no registries for the prescribers or for uninfected individuals taking Truvada for a PrEP indication.

There is no ICD-9 code that identifies an uninfected individual, if you will. And again, from what was displayed earlier, there is no documentation of safe use that is required in the REMS. Of course, the labeling; and as you've heard, and the earlier presentations can't

underscore enough, the importance of regular HIV testing.

Thank you.

DR. FEINBERG: Thank you very much, Dr. Yancey.

We will now break for lunch. It's 10 to 1:00. We will reconvene at 10 to 2:00. Panel remembers, remember you're not supposed to discuss this amongst yourselves or with anybody else. We'll see you at 10 to 2:00.

(Whereupon, at 12:49 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:50 p.m.)

Open Public Hearing

DR. FEINBERG: If everyone could please get seated, we'd like to get started again.

Thank you very much, everybody. We are on to the second half of our meeting. We're going to go directly to the open public hearing in order to keep the timeline for the public speakers close to what they were promised. And then we will have plenty of time for clarifying questions and discussion.

So let me open this part by saying both the FDA and the public, once again, believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes it's important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement to advise the committee of any financial relationship you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every

participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair.

You each have 3 minutes to speak. You will see a yellow light when you have reached 2 minutes and 30 seconds, indicating that you have half a minute left. We have 43 scheduled speakers. I will cut you off at the 3-minute point, so please pay attention to your yellow light because when it goes red, your time is over.

I would specifically really remind everybody that disruptive behavior such as shouting out or getting exercised about these proceedings is not in the best interests of all of us, and I will have to ask you to please sit down and not do that. And if you're not cooperative, I'll have to get one of the burly men in the room to help me.

(Laughter.)

DR. FEINBERG: So we're going to introduce people by their number. So will speaker number 1 step up to the podium and introduce yourself?

MS. LEATHER: I'm rather short, so -- this

thing is very tall. I don't have any financial, whatever that was that you said.

Thank you for allowing me to speak this afternoon. My name is Jan Leather. I am an RN. I've been an RN for 37 years. I've worked in England. I was educated in England. I've worked in Saudi Arabia for the Saudi military. I came to America and I worked for over 15 years in cardiac intensive care, and the last two years I've worked exclusively with HIV-positive individuals, both men and women, in South Florida.

I'm one of a team of three RNs. My roster is about 500 positive people in seven counties. We're in rural areas, cities, and towns. My clients' educational backgrounds range from not finishing high school to college-educated. My practice is HIV disease management. And I'm very nervous, but thank you.

My practice is in HIV disease management, education on HIV, safe sex practice, medication adherence, a monthly and quarterly basis dependent on the client's severity level. And we do annual

physical assessments in the clients' homes with the field nurses.

I'd like to speak about two of my clients who have been prescribed Truvada. The first is a gentleman of 52 years old who's been HIV-positive for the last 7 years who is noncompliant with his medication regime, not seeing his infectious disease physician, and has not been having any lab work drawn.

Oh, I've got 3 minutes. Okay.

The client recently went to see his infectious disease M.D. because of his hit-and-miss usage of his Truvada. His ID M.D. has now drawn a genotype resistance study. The client is having some opportunistic infections. He's going to have to wait until the 22nd of March to get the new results and to see whether or not he can continue to retake Truvada.

The client has not been taking the Truvada because of the side effects, especially the diarrhea. Even though the client has been HIV-positive for the last seven years and has been

educated about safe sex practices, I only spoke to him two days ago and he tells me he only wears a condom if his non-regular sex partners ask him to.

The second gentleman is -- he misses many of his doses of Truvada. He no-shows for his infectious disease M.D. appointments. And this client has relapses of alcohol and cocaine use and abuse. His priority is definitely not taking his medication.

For me, the most important things are finding out about the reasons they're not taking the medication, educating clients in adhering to the ways that their medication is prescribed, and helping clients to find solutions to make adherence easier.

For the safe sex practices, for me the irony is that condoms are effective, available, and cheap. And that's all I want to say. Thank you very much for letting me speak.

DR. FEINBERG: Thank you.

Speaker number 2.

DR ELION: Can I take her time and my own?

(Laughter.)

DR. ELION: My name is Richard Elion. I do clinical research at Whitman-Walker Health Center in Washington, D.C. I have served on the medical advisory board for Gilead, and our clinic does multiple studies with multiple pharmaceutical companies, including Gilead.

I speak today as a clinician, however, who's worked for the last 29 years on the front lines caring for men and women living with HIV. I've been busy working at Whitman-Walker, working in the nation's capital, since HIV was recognized in the early '80s, and I'd like to make three points and to reiterate some of the things that have been mentioned earlier.

The first is that PrEP works when people take the pills. The risk reduction when the drug is detectable is 92 percent and 90 percent in different studies, as was mentioned earlier, with overall efficacy ranging from 18 through 75 percent.

Second, I want to talk about the issue of

risk compensation, that there is currently -- and I think it was stated by both the FDA and Gilead earlier -- there's no data to show an increase in these risk behaviors.

We see here in iPrEx no increase in unprotected anal intercourse, and in another study looking at HPTN 052, where it was talking about treatment as prevention and where the discordant partner, the positive person, was treated with medication, there was no increase in risky behaviors as well.

I think you have two different studies here pointing out that you don't see increases in behavior despite there being the ability for medicine to help people feel a sense of protection. There's no data in these two studies, as well as others presented earlier, that we see these kind of increased behaviors in those settings.

Third, and this had been pointed out earlier, I think we have to be very candid that we talk about how wonderful the various prevention strategies we have are, that essentially, that when

we start at the top of the people who already are HIV-positive and we look at the total successes -- and this rate is 23 percent success rates at getting HIV suppressed; in Washington, D.C. in the last couple days, there was data presented that shows that our numbers are only running about 18 percent of the overall population -- the need for prevention is incredibly, incredibly important.

Let me bring this down to a community level. A 22-year-old man who came to see us last week who gets high when he has sex and doesn't want to use condoms despite eight years of education otherwise, since he's 14; a 57-year-old man with erectile issues who hates condoms and figures he can live out the rest of his years with HIV; or the 18-year-old female who's been in an abusive relationship and can't get her partner to use condoms without threats of violence. These are common cases of what we see at Whitman-Walker. These people are at risk for contributing to new cases of AIDS. They need a new care plan, a new approach that works.

Finally, what we need currently is

additional tools for our toolbox. We're not winning the battle and we --

(Microphone turned off.)

DR. ELION: It's giving me 60 seconds. I'll be done. I need to take it.

So the point I want to make is that we can see the success of decline in incidence rates with subsequent additions to the toolbox. Please, what we're asking today is to allow a modality that still is being developed, that still needs further work, to be able to be added to our toolbox.

DR. FEINBERG: Dr. Elion, you need to stop now. Thank you.

DR. COX-IYAMU: Hi. I'm Roxanne Cox-Iyamu. I'm an infectious disease physician, and I treat patients at AIDS Healthcare Foundation. I have over 20 years' experience treating HIV-positive individuals, patients who are uninsured and underinsured. And I am here for purely selfish reasons.

I'm here because my patients think I walk on water. And the reason they think I walk on water

is when I prescribe them the very-easy-to-take Atripla and they take their medication, they get better and they stay well and their viral load stays down.

So, as I said, the reason I'm here is to ask you all to seriously consider, do we have enough information to approve Truvada as PrEP? I'm concerned about the potential for development of resistance. I'm concerned about the resources that providing Truvada will take away from monies we're using to treat HIV-positive individuals. And I'm concerned as a black woman that we don't have enough data that -- I'm sorry for this -- that this actually works in women.

The iPrEx study and the CAPRISA study actually look very good. To date, there have been three studies on PrEP involving women, all three insufficiently powered to be pivotal trials in support of a new indication as broad as the one Gilead seeks. At best, they provide only collaborative support.

None of the results over these trials have

been published or peer-reviewed, and we are unaware that the raw data has been made public or provided to the FDA.

The first of these trials is the FEM-PrEP study, this study only in women. It was stopped mid-trial because a preventive effect of Truvada could not be established, and the number of individuals who were HIV-positive were equal in the placebo and the treatment arm.

There was the TDF2 study, a 1200-participant study which studied PrEP in both men and women. This trial had to be adapted, and the data may never be available for evaluation.

This leaves us with the Partners PrEP study. In this study, there are some flaws. The flaws include that 20 percent of the HIV-positive partners were already on antiretroviral therapy. This is a confounding circumstance that would reduce the likelihood of infected persons transmitting the virus.

In light of the limited data we have as far as women are concerned, again, I ask us all to be

responsible stewards of the public health and to consider the scientific data in approving PrEP for pre-exposure prophylaxis. Thank you.

DR. FEINBERG: Speaker number 4.

MR. ELLIOTT: Good afternoon. My name is Robert Elliott. I'm a registered nurse. I'm an active member of the American Nurses Association and serve on the Congress on Nursing Practice and Economics. I'm also involved in the ANAC, Association of Nurses in AIDS Case. I've worked with HIV patients for a couple of decades as a volunteer as well as a registered nurse.

There is no question that if efforts on using PrEP are widespread, condom use and other means of preventing HIV infection will decrease. In this area, as many areas of life, risk compensation is real and risk compensation is documented.

Already, increases in risk behavior have been documented in the HIV vaccine trials, HIV microbicide trials, and among HIV-positive patients who believe that the HAART treatment protects

against transmissions.

Moreover, in a study looking specifically at any connection between the use of PrEP and risk compensations, men who have sex with men in New York City, provided a description of PrEP and asked if they were likely to be using PrEP, of those saying that they were likely to use PrEP, over 35 percent said that they would be likely to decrease condom usage while on PrEP.

Finally, other studies among men who have sex with men, injection drug users and heterosexuals, have shown that the mere promise of expanded access to treatment or a post-exposure prophylaxis has been associated with significant increases in risky behavior.

Given the lack of adherence demonstrated in iPrEx, many people ostensibly taking PrEP will not use any preventive health measures. At the same time, many of these same people will decrease condom usage or engage in other risky behavior, which can lead to increase HIV infections as well as STDs and parasitic infections.

At this point, we simply don't know enough about how to increase adherence rates to work with the PrEP and how to contract -- or, excuse me, how to counteract risk compensation in the use of PrEP. Until such studies are done and until we obtain this knowledge, PrEP is not and cannot be considered safe and effective for preventing HIV infections.

I thank you for your time, and -- I should have said this at the start -- I have no financial interest with any pharmaceutical company. But I do hope that we seriously consider the things that I've said. Thank you very much.

DR. FEINBERG: Thank you.

Speaker number 5, please.

MS. HAUGHEY: Good afternoon, everyone, and thank you for this opportunity to speak. I have no affiliation with anyone here.

My name is Karen Haughey. I'm a registered nurse in the state of Florida and in Washington, DC. I am also a certified legal nurse consultant, a national member of the Association of Nurses in

AIDS Care, and my experience has been in the ER, in home health, and in HIV/AIDS disease management.

But human nature is really the reason I'm here today because human nature, I believe, is the reason that Truvada will not work as a prophylaxis medication. It is not in our nature as human beings to always do what we are told 100 percent of the time.

Truvada needs to be taken every day, 100 percent of the time, and my experience as an RN has shown me that this just won't happen. In the eight years that I have cared for patients, across the board it's been difficult for them to stay adherent. And these are sick people. These are people with HIV and AIDS. They have a life-threatening illness, but not one, not one patient that I have cared for, has been able to be 100 percent adherent.

I'd like tell you about one patient of mine. I used to go to his home several times a month to fill his pillbox, check his missed doses, and he missed doses frequently because of the side

effects. He took Truvada, which not only exposed him to problems with renal issues, but it pretty much guaranteed him daily diarrhea. And this is the kind where you need to know where the bathroom is all the time. And there were days when he simply didn't know where the bathroom was all the time and needed to be out, so he missed his doses.

Now, we might all think that this isn't a big tradeoff for a med that's going to save your life. But I ask you, how do you justify that when you don't have HIV, when you aren't sick, and what you are taking will damage your kidneys and give you diarrhea every day?

People aren't going to take Truvada every day. And then they're going to think that they're protected. It's not in our nature as human beings to take pills when we're not sick. How many of us really and truly finish that 10-day course of antibiotics? How many of us take our blood pressure medicine every day, our cholesterol pills every day? I myself have a grandchild because my daughter was on daily birth control medication.

In order for Truvada to work, it must be taken every day. If you skip a dose, the door is open for resistance, effectively stopping Truvada from being used as an ARV therapy if you do become infected.

So I ask you simply to consider the reality of human nature, and how approving Truvada won't help people but may set them up for getting the disease they think they're preventing. Thank you.

DR. FEINBERG: Thank you.

Speaker number 6, please.

MS. KELLER: I'm Joyce Turner Keller, a minister and AIDS activist. I care about this issue because of the impact that it will have on the community in which I live and work.

I started a nonprofit from my Social Security check after being diagnosed positive as an AIDS-infected woman. I've spoken before Congress as an advocate, served as the national co-chair of the Campaign to End AIDS, and I sit on the board of directors of ADAP Plus. I disclosed my status to the world in a PSA. I'm a certified counselor. I

do testing and provide education to people who live and are exposed to the issues of HIV and AIDS.

I tested positive in 2001, disclosed my status within four hour sort of knowing that I was positive, and I've taken my message from the pulpit to the public. I work in Baton Rouge, where currently we are weight number one per capita with new cases of AIDS infection, according to the CDC. Young blacks and females are at a greater risk of infections. I work with college students, recovering addicts, churches, preteens, and teenagers, senior citizens of all races, creeds, and colors.

The greatest obstacle I face in addressing the HIV/AIDS epidemic in my community is the attitude of invincibility. Everyone believes that they are exempt from this virus. It will only happen to someone else. I'm only sleeping with one person. I'm a praying man/a praying woman. I'm church-going. I'm married. I have my tubes tied, one young woman told me when I offered her condoms. I'm too young, or I'm a senior citizen.

Before approval of this drug and its release in my community, there must be more research and a mass media campaign in communities of color outlining the dangers of the risky behavior and the use of PrEP. The inability to negotiate condom use is a large problem in many communities, and it will become even more difficult.

Based on my experience with my community in which I live and work, PrEP will open a floodgate for risky behavior. We'll have people refusing to use condoms because they believe PrEP is a fix-all and a cure for HIV.

What I'm asking you today is, if you're going to light fire to my community, please allow me to see the fire engine sitting where I can put out the fire. Thank you.

DR. FEINBERG: Thank you very much.

Speaker number 7.

MS. JACKSON: Hello. My name is Miki Jackson. I'm an AIDS advocate. I am not affiliated with a drug company except, of course, that I do pay very high prices for anything I need,

like everyone else.

A recommendation for use of Truvada as PrEP is akin to issuing an engraved invitation for lawsuits and legal action. It puts this agency -- to speak of not all the other things it puts in that way -- in a legally very risky position.

From colas laced with cocaine through thalidomide in the '60s to the recent debacle of Vioxx, carelessness at this level comes at a high price for the FDA, its reputation, the government, and, most of all, the public.

To knowingly recommend a drug as powerful as Truvada with such serious, serious known side effects to be given to people who are perfectly healthy is frighteningly reckless. To do so when the studies are so limited, still have so many questions about them, not to say, let's take a moment and do some more studies, let's find out more about women, I think is inexcusable.

To do so without going far more through a lengthy and thorough, really thorough process is inviting disaster, setting oneself up for being

called reckless. To do so with no requirement for HIV testing, for proper medical supervision and follow-up, is a shameful disregard for performing the minimal duty of protecting the public.

The creation of the FDA, which sprang from the 1906 Pure Food and Drug Act signed by Theodore Roosevelt, who knew a few things about corporations, signaled the official recognition of the need to protect the public from harm based on a long history of profit-driven drug makers, from the days of crude traveling medicine shows selling snake oil to sophisticated modern pharmaceutical giants with smooth marketing campaigns.

This abbreviated process with so little transparency, public records release even being denied, will put this agency in an untenable legal position.

DR. FEINBERG: Thank you.

Speaker number 8 isn't here, so we'll go to speaker number 9, please.

MR. TERRILL: Good afternoon. My name is Joseph Terrill. I do not have any financial

relationship with the makers of Truvada.

Currently, I am the domestic advocacy manager for AIDS Healthcare Foundation. My advocacy work at the grassroots level started over 25 years ago, when the impact of AIDS first hit the gay male community and forever entered our consciousness.

But I am also a gay man who has been living with HIV for 32 years. My current drug regimen, which controls the HIV from replicating in my body, includes Truvada. While I am grateful that this drug exists, and in my particular case appears to work well, I am here today to express my concerns about this additional application for using Truvada as PrEP for those gay men who are HIV-negative.

For most of us within the gay male community, negotiating safe sex and the surrounding complications that comes with it has become a routine part of our daily life. It has been and continues to be difficult for many of us.

We are tired and annoyed with that reality. My community has reached what I call condom

fatigue. Many of us yearn for the day when concerns about condom use and worried about transferring the virus to others becomes a thing of the past.

It was with great anticipation that I read about the PrEP studies, wanting to embrace a new preventive tool. But the more I read, the more I was disappointed. If this was the answer to condom fatigue, I'd applaud this new application. But the ability of people to adhere to a daily regimen of taking a drug is difficult. The studies show that quite clearly.

As much as I try to stay consistent in taking the drugs that I know are keeping me alive, and as educated as I am about adherence, I have missed doses. I also worry about the long-term side effects to my kidneys and regularly have blood work done to monitor its effects.

In all my conversations with gay men about PrEP, its focus has been on not having to use condoms any more. I fear that men will take the drug inconsistently, have a false sense of

security, and increase risky behavior.

Currently, individuals who are at risk can get Truvada prescribed for off-label use. If we rush to approve this application, men who take it incorrectly, thinking of it as a party drug, will tend towards developing resistance to the drug and increasing the likelihood of generating a Truvada-resistant strain of HIV.

My concern is based on those participants in the study who were paid, counseled, and regulatory monitored, and were still not able to adhere to the prescribed dosage. In a real world scenario, how much more likely will that be the case?

We need to slow down. I care too much about my community to not speak about my concerns. Thank you.

DR. FEINBERG: Thank you. We're going to fix the podium here for a moment.

MR. MYERS: Good afternoon. My name is Tom Myers. I'm general counsel of AIDS Healthcare Foundation --

DR. FEINBERG: Could you wait a second? My

understanding was they were going to fix the podium.

MR. MYERS: Oh, I'm sorry. Can we get this reset, then, please? Great.

DR. FEINBERG: Okay. I'm sorry. Go ahead.

MR. MYERS: Good afternoon. My name is Tom Myers. I'm general counsel of AIDS Healthcare Foundation, a position I've held for the past 13 years. I'm also the author of a citizen's petition that has been submitted to this committee. Although I know you're quite loaded down with materials, I hope you'll be able to take the time to review it.

With respect to PrEP, I think it's helpful to remember the first rule of medicine, do no harm. Also, given the few small studies on which this application is based, the many things we still do not know regarding adherence, risk compensation, kidney damage from long-term use, and the many studies studying PrEP still in the pipeline, my question is, what's the rush?

I know we have an epidemic. But a quick,

ill-considered approval would not quickly end it. People who may take PrEP aren't sick. They are well. And yet the proposed indication is that any adult in America may take Truvada, a drug known to be highly associated with kidney damage and other side effects, for PrEP. And they must take it every day to gain some preventive effect.

This application is based primarily on two small studies. In one, iPrEx, a majority of the study participants, despite monthly, massive, hands-on counseling, did not take Truvada every day. However, FDA in its REMS seems to believe that this large-scale adherence failure can be overcome by distributing educational brochures and wallet cards.

Everyone concedes that PrEP must be part of an ongoing, comprehensive counseling and other intervention services. By and large, these do not exist in the United States, and the proposed REMS does not require it. Absent these interventions, PrEP has not been found to be safe and effective.

All the data presented today confirms that

if you are younger or less educated or poor, you will have great difficulty adhering to this drug. Younger, less educated, and poor precisely describes those in America most at risk of contracting HIV. This will not work for them.

At this time, there simply is not enough evidence to establish safety and efficacy, not enough evidence to unleash PrEP into wide-scale use. And FDA in its REMS seeks the widest possible access.

This is the antithesis of do no harm. There are at least eight more studies of PrEP underway, and hopefully these will fill in the missing pieces of information. Until that time, PrEP should not be approved.

I would welcome any questions that you have. Thank you.

DR. FEINBERG: Thank you.

Speaker number 11 is not here, so we'll go on to speaker number 12, please.

DR. CHIEN: Good afternoon. My name is Catherine Chien. I'm a physician specializing in

HIV infection, practicing for close to 10 years, and currently caring for over 500 HIV-infected individuals in the downtown Los Angeles area. I will disclose that I attended a one-time meeting with Gilead. It was a medical advisory board on this specific topic of Truvada as PrEP.

I'm not here to argue the efficacy of Truvada as PrEP. The iPrEx study clearly showed that among individuals who actually took the drug, there was a relative reduction in HIV risk of 92 percent. Yet in the overall analysis, this value is much less, only 44 percent. Why?

Because patients didn't take the drug daily as prescribed. Keep in mind, this is even among patients motivated enough to participate in a clinical trial, a trial in which, as mentioned earlier, participants received counseling every 4 weeks. What happens when we translate this into the real world? In my opinion, we'll see an even lesser benefit.

I'm an HIV provider. I have a hard enough time convincing my patients with HIV to be adherent

to their medications daily. Now imagine a primary care family practitioner, who has little or no experience with HIV, trying to convince his HIV-negative patient to take a medication every single day to prevent something that he may or may not expose himself to on those few occasions he chooses to have unsafe sex, or the many occasions.

Guaranteed, this real-world scenario will look very different than what study participants were exposed to every four weeks when they participated in iPrEx. So how will this translate into an actual real-world benefit of PrEP?

This leads to my second concern. If patients taking the drug don't fully comprehend the importance of daily medication adherence, what are they likely to do? My best guess is that they'll take the drug when they think they need it, after a crazy weekend of partying, or maybe over the entire weekend, knowing they're planning to engage in unsafe sex.

As we learned from iPrEx, this sporadic dosing won't provide nearly as much protective

benefit as the patient may think he's getting. And worse yet, this individual may have a false sense of protection, leading to risk compensation: decreased use of condoms, higher-risk sexual behavior.

Also, if this individual thinks he's taking something that's protecting him from him, might he be less likely to seek HIV testing because of this perceived lower risk? In my opinion, this could lead to higher rates of HIV transmission and higher rates of HIV drug resistance if this individual contracts a virus, doesn't get tested, and continues sporadic Truvada dosing.

Lastly, I'm concerned about the potential impact this will have on my patients who are already living with HIV. My fear is diversion, diversion of Truvada from patients who should be taking it as part of their HIV cocktail to HIV-negative persons who are willing to pay to get it from someone on the street rather than deal with the hassle of going to a clinic, getting lab work done, and so on. There's already a street value

for all types of prescription drugs. What if Truvada suddenly had that value?

DR. FEINBERG: Thank you.

Speaker number 13 isn't here, so we'll go on to speaker number 14, please.

MR. LACHARITE: Good afternoon. My name is Chris Lacharite, and I'm grateful to be able to speak before you today.

I've been working with persons with HIV since 1986, where I opened the first HIV program at Brigham and Women's Hospital in Boston. Since that time, I have taught, practiced, managed, and published about HIV, and worked in various cities such as Boston, New York City, Los Angeles, and South Florida.

I have a master's degree in community health nursing and an ABD for a PhD in nursing science, specializing in LGBT health. We are concerned -- and I have absolutely no affiliation with the sponsor of this -- the sponsor or any of its competitors.

We are concerned about the cost and public

health implications of the extremely large number of people who will have to take Truvada for PrEP to prevent just one infection. While the relative risk reduction found in the iPrEx study may have been 44 percent, the absolute risk reduction was only 2.3 percent.

This distinction is critical because in order to prevent just one new HIV infection via Truvada for PrEP, approximately 45 people will have to be taking Truvada for PrEP.

As a simple cost analysis, this means the cost of preventing just one HIV infection over a one-year period of time will be well over $500,000. This figure is approximately 20 times higher than the cost of treating an HIV-positive person for one year, which treatment reduces the relative chance of infection by 96 percent, much more than PrEP.

In addition, this does not mean only 45 people will need to take Truvada for PrEP. It means 45 people taking Truvada properly with daily adherence, something which the data show many will not do. As many, if not most, people will not be

adherent in order to prevent just one new case of HIV transmission. Many more than 45, given the 46 percent nonadherence rate in the iPrEx study, perhaps double that number, will need to take Truvada as PrEP.

It is clear that for Truvada to have any impact on HIV prevention, many otherwise healthy, noninfected persons taking Truvada will experience some level of kidney disease and other harms.

The likelihood of kidney damage, as well as the likelihood of increased HIV infection, due to poor adherence and increased risky behavior, and the likelihood of development of Truvada-resistant HIV strains all rise substantially in this larger population, and all for the goal of preventing one single HIV infection.

Again -- thank you.

DR. FEINBERG: Thank you.

Speaker number 15, please.

MS. NASH: My name is Elizabeth Nash, and I have no financial disclosures. I have been a nurse for 16 years. I have specialized in the following

areas of critical care, hospice and palliative care, and HIV/AIDS nursing. I am an ACRN, which is an AIDS-certified registered nurse, and I'm licensed to practice in Florida and the District of Columbia. I also hold a master's degree of public administration, and I've been a local and national member of the Association for Nurses of AIDS Care Today for ten years.

The pivotal study underlying this application, the iPrEx study, found Truvada as PrEP, pre-exposure prophylaxis, correlated with only a 44 percent relative decrease in HIV infection. In order to determine whether this intervention is effective in preventing HIV transmission, it must necessarily be compared to alternative methods of preventing the infection.

The iPrEx study did not includes individual who engage in heterosexual sex, inject drugs, or other high-risk populations such as incarcerated individuals. Whether 44 percent relative efficacy may be considered effective for treating an actual illness or condition, especially if the alternative

is the worsening of that condition, 44 percent seems quite low for an intervention that is meant to be preventive. And I believe other people may speak to how that even 44 percent will not be repeated outside of study conditions, which included intensive risk reduction counseling, frequent screenings for HIV and STDs. In the real world, that won't happen.

It's hard to think of other preventive measures, such as birth control or vaccines, where 44 percent relative efficacy is deemed effective. This lack of efficacy is even more apparent when compared to existing means of HIV prevention, such as condom use.

Condom use has been the virtual gold standard of HIV infection prevention for decades. The ability of condoms to prevent transmission of HIV has been scientifically establish in laboratory and epidemiology studies of HIV-negative and unaffected persons.

Pinkerton and Abramson's 1997 analysis of 11 separate studies published since 1987 concluded

that consistent condom use reduces HIV transmission by 95 percent. None of this data this far offered in support of Truvada for PrEP even approach demonstrated effectiveness of the condom.

In comparison to the long history of very -- thank you.

DR. FEINBERG: Thank you.

Speaker number 16 is not here, so speaker number 17, please.

MS. AARON: Good afternoon. My name is Erika Aaron, and I have no financial conflicts. Thank you for this opportunity.

I'm a nurse practitioner who has provided clinical care to women in HIV since 1989. I have been a member of the DHHS Perinatal HIV Guidelines Committee since 2006, although I'm not representing the opinions of this committee.

I do represent a network of clinicians offering comprehensive reproductive healthcare to women in various settings around the United States, and we believe that Truvada PrEP indication should be approved for HIV uninformed women. Let me give

you some examples of women who have recently come to me concerning advice about the use of PrEP.

One woman, who is HIV-negative and in a long-term relationship with a patient of mine who's HIV-positive, came to me two months ago after sporadically using his Truvada during pregnancy attempts without any medical monitoring. Happily, she had a positive pregnancy test, and she had no adverse reactions. And she had an HIV-negative test.

She continued PrEP throughout the prenatal period to avoid primary HIV infection during pregnancy since there is a known increased risk of acquisition of HIV during pregnancy and a very high risk of transmission to the infant due to seroconversion during the prenatal period. I advocate for approval of Truvada for PrEP during pregnancy for couples who are unable to negotiate condom use.

Another woman from West Africa who's HIV-negative and has a husband who's HIV-positive came to me for information about fertility. She went to

a fertility clinic and was told that she had to pay for artificial insemination, which would be $12,000. She could not afford that, and she asked me to provide PrEP in order to attempt pregnancy attempts.

Then there's Al. I've known Al since he was an infant. I took care of his mother, who died one year after he was born. Al has brought himself up on the streets of Philadelphia with very poor adherence to ART, resulting in acquisition of multiple resistant variants.

I saw him just yesterday with his partner, who is a bright, supportive young woman who has been helping him take his ART. His CD4 count is 4. And she asked me, what else can I do besides condoms -- he has a hard time using them -- to protect myself? I would like to offer her Truvada.

As always, in the history of HIV care, our patients are leading the way. The results of the trials that have been presented to us, I feel, are very reassuring. PrEP use in stable serodiscordant couples may result in high adherence due to

motivation to reduce the risk while preserving a partnered relationship.

Additionally, the use of PrEP during conception attempts is promising in that the motivation for adherence is high. There are an estimated 140,000 heterosexual --

(Microphone turned off.)

DR. FEINBERG: Thank you.

Speaker number 18, please.

MR. FISHER: Good afternoon. My name is Herb Fisher, and I have no conflict of interest. I want to thank the members of the committee for holding this hearing and allowing my VOICE to be included in the evolving debate surrounding this important treatment as prevention issue.

I have witnessed the full progression of HIV since its inception, including losing a partner to AIDS on a cold San Francisco morning in 1988. During the ensuing 24 years of living with HIV, I've taken almost every cocktail of meds imaginable as they became available until my virus eventually mutated a resistance to them, including Truvada,

just as it has, surely, in many other HIV-positive individuals.

These, plus my 12-year personal experience with real-life challenges that make adherence to taking HIV meds almost impossible, even when those whose very lives depend on it, are significant facts that render the current PrEP proposal useless in protecting anyone against existing Truvada-resistant HIV. More importantly, they legitimize concerns of whether or not the 44 percent efficacy achieved during the original PrEP trials, which were operated with controls unlikely to occur in real-life applications, are far more optimistic than attainable.

Therefore, I implore the FDA to consider the adherence experienced voice of reason for denying approval of PrEP until more research justifies the risks and costs to public health policy, especially at a time when limited existing funds should be more wisely spent on treating those already infected who are languishing on the nation's shameful ADAP waiting lists.

Thank you for your kind consideration.

DR. FEINBERG: Thank you.

Speaker number 18, please.

MR. MYERS: Good afternoon. My name is Kirk Myers, and I have received financial support for travel from Gilead Sciences.

I am the founder and chief executive officer of Abounding Prosperity Incorporated, an indigenous grassroots organization preventing HIV in Dallas, Texas. I'm also a black man who has sex with men, MSM, who is living with HIV, and in a serodiscordant relationship.

Through my lived experiences in managing my own disease and the leadership experience of managing an agency dedicated to decreasing new incidents of HIV via various prevention efforts, I know that delays and deliberations that are surrounding the prompt review of PrEP in black MSM and transgender male-to-female individuals is out of synch with our real world.

The urgency for the black community, particularly in the South, which has been

disproportionately impacted by HIV and AIDS, is more and varied prevention efforts. For me, simple language best captures the reality among my people, especially those black MSMs and transgender individuals in the South overwhelmed by the social, economic, and health disparities they confront on a daily basis.

So while some people have privilege on their side for a time-consuming contemplation over the prompt review of PrEP, my community makes immediate choices on a day-to-day basis that ultimately could result in the acquisition or spread of HIV.

Therefore, I urge the prompt approval of PrEP because it is right to give black MSM and transgender people the option to make a choice on a daily basis to protect their lives as we go about our business as usual. Whether our business is at the level where I work as a CEO or the street level of a sex worker, I will be standing as an authentic voice to compel the advisory committee to consider the fact that I have immediate access to those who would benefit from PrEP. I have organized the

community forums, focus groups, and one-on-one individual-level interventions to speak with authority that this drug is wanted.

The young black gay men who confide in me have expressed receptivity to a drug that has the potential to protect them from HIV and AIDS. And quite frankly, we need more tools on the front line to prevent HIV where I live and work, and PrEP is just that, another tool we can use for those that are most vulnerable.

Finally, if anything is right at this historical moment, it is the option to go beyond the past practice of normalizing the majority and ignoring the pressing needs of the minority. The right thing to do is to empower black MSMs and transgender individuals with additional tools on a daily basis that are purposefully designed to protect public health.

Without this option, expediency, desperation, and ignorance will continue to drive up the statistics of new incidence of HIV and AIDS, not only in the South but nationally. With all due

respect, I am asking the advisory committee to join me in doing the right thing and insist on the prompt approval of PrEP. Thank you.

DR. FEINBERG: Thank you. We'll take a pause for a moment; they're going to fix the podium there.

(Pause.)

MR. KENSLEA: Good afternoon. I'm speaker number 20. My name is Gerard Kenslea. I have no conflict of interest, and I am the communications and marketing director for the AIDS Healthcare Foundation, where I've served for the past 16 years.

I'm here today to express my grave concerns about the possible approval of Truvada for a form of PrEP. Specifically, my concerns involve the ultimate real-world deployment and application of this pill, should it be approved. I believe these concerns are well-founded.

Last year, in response to the news that the iPrEx study showed some efficacy in preventing HIV, AHF hired an outside third party research firm to

conduct an online exploratory survey of a diverse group of men, 822 gay, bisexual, MSM, and transgender individuals to determine how this medication would be used in a real world situation.

Our survey consisted of 13 multiple choice questions, and the following introduction was given. "Consideration is being given for approval to give an HIV medication to people who are HIV-negative to prevent them from becoming infected with HIV. This survey is designed to determine how the medication would be used in a real-world situation."

Our survey was first presented at an HIV PrEP symposium at UCLA and was designed specifically to determine real-world reactions from prospective consumers of this drug about taking PrEP to gain further information about potential adherence issues to the pill and the possible impact on condom use.

Among the key findings of our survey, 79 percent of respondents said yes, they would take a pill on a daily basis if it could prevent HIV.

However, that number dropped to 63 percent of respondents who said they would actually be very likely to actually take the pill and remember to take the pill every day. That number plummeted to 41 percent when people realized if they needed to have frequent doctor visits, if they had to have labs drawn, or have a copay of any sort.

These results suggest a need, really, to gather more real-world information on the use of PrEP before FDA approval. The survey raises real questions about the use of PrEP, particularly with regard to adherence and the public health implications of decreased condom use.

In light of recent research proving a 96 percent reduction in transmission when HIV-positive patients are on treatment, we in the AIDS community must ask where the research should be best deployed. Thank you.

DR. FEINBERG: Thank you very much.

Speaker number 21, please.

MR. ROSE: I just want to say, ladies and gentlemen of the committee, I'm honored for the

privilege to speak before you today. As a young black HIV-negative man, I represent one of the most at-risk populations in this country.

Just last summer, the CDC released new data that underscored the impact of the HIV epidemic among young black MSMs with a shocking 48 percent increase in new infections in the populations. Yet studies have shown that young black gay men are no more risky in terms of their sexual behaviors than their peers. As a young black gay man, I have known that this data would say just that and present a very grim picture for my community.

The real truth is that the current prevention package isn't working for us, isn't meeting the needs of the young black gay experience, isn't doing its job, because 48 percent increase would tell you otherwise.

So what I ask you today is that given that the current model of prevention is insufficient at turning off the faucet of incidence rates, I ask you today to give the promise of my community that we have another option. And I'm not here to say

that a single drug or single strategy will ever end this epidemic for us. What I'm asking for you is to allow people to be met in the real locations of their lives, to give them options and choices, to figure out prevention strategies that work for them, because condoms and DEBIs aren't doing it. I ask you today to look at tools and evaluate things that science tells us will give us a chance at making a change to the epidemic.

As a young black gay man, I am highly aware of the potential concerns of PrEP. But the idea that my community can have something better excites me. It excites me friends. While we might not represent the average PrEP user, we firmly believe that PrEP gives us an opportunity and a chance to believe that science can give us hope for our community, and lets us believe in one of our favorite people, President Barack Obama, who himself said, "When the United States will become a place where new HIV infections are rare." And we believe that PrEP is the chance and the opportunity to reach that hallmark.

We're asking today that you give us a reason and a rationale to support your decision based on scientific numbers, data, and evidence, and then tell us why, in language that we can understand, about how you got there; but more importantly, that you recognize and underscore the problem and the impact of the epidemic on my community. Because there are only so many brothers I can see tell me they're positive, so many more people I know that can tell me that they don't think they're going to live to see 50 even with drugs available because they can't afford them.

So I ask you today to make a decision based on numbers, science, and data that gives hope to people who are looking for just that.

DR. FEINBERG: Thank you very much.

Speaker number 22, please.

MS. GRUTTADAURIA: Good afternoon. My name is Jessie Gruttadauria. I am the director of public health and domestic advocacy for the AIDS Healthcare Foundation, and I do not have a financial conflict.

I've spent the past 22 years of my life caring and advocating for people living and dying of HIV and AIDS. There are a few people here, friends and coworkers, who take Truvada and have lived very, very healthy and productive lives. It has been a very good drug for people who are infected. I've been very, very fortunate to watch -- and one of the speakers will be up shortly -- watch his life unfold in unimaginable ways.

People living with HIV have to live with both the side effects and the realities of adherence to medications. It can be a struggle and challenge for them. And these are people living with the disease. In my experience, it is not rational to expect that people who are otherwise healthy would find it any easier to adhere to this chemotherapy.

If the indication for this application is for men who have sex with men, is it nor reasonable to expect that women will also want to access this medication to protect themselves as well? There's

no way that gay men, for instance, will be granted access but women of color will not.

We know that the FEM-PrEP was stopped because it was not showing a benefit. We also know that some men who have sex with men have sex with women. We cannot create an inequality in access in this way.

In short, your decision to open this unproven treatment for any one population opens it for all. There's more work to be done. There are more trials that are relevant to populations in the U.S. to be done. The implications to prevention work in this country are too great to act hastily here. I urge you to reject this indication and revisit it when the work has been done and the questions -- even the proponents of PrEP acknowledge are unanswered.

In the meantime, we can continue to identify HIV-positive people, assist them into treatment, where we know if they are virally suppressed there is genuine benefit to them and their partners. Thank you.

DR. FEINBERG: Thank you.

Speaker number 23, please.

DR. CHEN: Good afternoon. I have no relevant financial interest to disclose.

My name is Wayne Chen. I am a doctor working at AHF healthcare centers in Los Angeles. I'm also the director of the managed care department.

I'd like to voice my position that I am against Truvada as pre-exposure prophylaxis. I'd like to direct the panel's attention to the iPrEx study, where almost half of the study participants had no detectable blood of Truvada when the number should have been closer to 100 percent. Based on this data, we can reasonably anticipate that people would not take Truvada as prescribed on a daily basis.

My concern, as well as others, is what this demonstrated lack of adherence would mean for HIV drug resistance in the future. Today Truvada is the front line treatment for HI V infection, and it's the most prescribed HIV drug in the United

States. Should its use for PrEP become widespread, potentially millions of people at risk for HIV will be taking Truvada with varying adherence, and this is unacceptable.

Even now, drug resistance is a growing concern in HIV treatment. As the transmitted resistance rate is 15 to 18 percent among newly HIV-infected persons. If Truvada for PrEP is added to the mix, this becomes even more alarming. And this concern is well-documented.

Two patients already infected with HIV in the iPrEx trial developed resistance to Truvada. Given the FDA's REMS proposal, that people not be required to screen for HIV prior to initiating PrEP or to be required to be monitored thereafter, and given the data documenting poor adherence even under ideal study conditions, there is a real risk that patients will take Truvada inconsistently, contract HIV, and then not be able to have Truvada available to them as a first line effective therapy because they've developed a drug resistance already to it.

Let me state clearly: As a physician, I have qualms about prescribing PrEP when there is a safer, more effective condom alternative that does not bring these kinds of risks to the patients. PrEP puts the patients' health at risk and is contrary to the Hippocratic Oath of doing no harm to the patients.

Even more alarming than the development of a drug-resistant patient is the development over various strains of Truvada-resistant HIV, which could be passed on to others. As stated before, Truvada is one of the most prescribed HIV drugs in the United States. The development of Truvada-resistant strains of HIV would make battling the AIDS epidemic even more complicated and costly, especially given this era of healthcare reform and limited financial resources on all levels.

Thank you very much.

DR. FEINBERG: Thank you.

Speaker number 24.

DR. KHANLOU: Good afternoon. Thank you, the honorable members, allowing me to come here.

My name is Homayoon Khanlou. I'm a physician and also a principal investigator on clinical trials at AIDS Healthcare Foundation. I have worked on several Gilead studies, but not on the iPrEx and PrEP. I would like to point out to the members a couple of issues about iPrEx trial.

The iPrEx trial, which was studying Truvada as PrEP only in men who have sex with men, is a pivotal study offered to support this application. Therefore, the size, scope, and rigor of this study must be closely examined, especially for an indication for a population of potentially healthy millions of unaffected people who will be using this drug who has significant risk factors and risk profile.

We urge this panel, which is tasked to advise on scientific and biostatistical matters, to take rigorous and make it rigorous analysis. Especially, we urge close examination of the statistical analysis of the study, which appears to be insufficiently powered to support the proposed indication.

Historically, FDA looks at ICH guidelines as a benchmark for determination of the study size. Those guidelines typically call for a minimum of 15 patient exposure for a study like iPrEx. The iPrEx study barely made the 15-patient exposure.

Given the proposed indication and the contemplated long-term use of Truvada, it appears that even 15 patient exposure will not be sufficient. Because of this new indication, we would ask the committee to consider that even 15 patient population exposure may not be sufficient to show clinical significance.

Further, it is unclear that the study findings of 44 efficacy [sic] met the protocol original measurement of efficacy. As is stated in FDA brief, page 36, it cannot be ruled out that the actual efficacy was below 30 percent, a predetermined level for clinical significance. Thus, even though the results are statistically significant, they may not be clinically significant.

Finally, the study's geographic location and

demographic may not allow for any findings to be generally adaptable to the other side of United States. Fewer than 10 percent of the study participants were black. Given the fact that the most vulnerable patient population and people are African Americans, this may not be applicable to this community and others.

We strongly urge FDA to consider a rigorous analysis of the statistical model and evidence submitted for this trial. Thank you.

DR. FEINBERG: Thank you.

Speaker number 25, please.

MS. DAWSON: Good afternoon. My name is Lindsey Dawson, a public policy associate at the AIDS Institute, a national nonprofit organization providing leadership in HIV/AIDS public policy, research, advocacy, and education.

Today we offer our strong support for the efficacy supplement for the drug Truvada, to include indication for pre-exposure prophylaxis, PrEP, to reduce the risk of sexually acquired HIV-1 infection.

While there are approximately 50,000 new infections each year and 1.2 million people in the United States living with HIV/AIDS, for the first time and end to the epidemic is in sight.

In order to realize this, it's critical that we expand prevention, screening, and HIV/AIDS care, treatment, and all interventions proven to be scientifically valid and evidence-based and at the forefront of our efforts. We believe that the evidence submitted by the applicant for Truvada places PrEP solidly within this arsenal.

As a result of multiple studies, we know that the use of PrEP effectively reduces the risk of HIV infection when taken on a regular basis. The Partners PrEP study found Truvada reduced HIV infection by an estimated 73 percent. The TDF2 study found a 63 percent reduction in the study population overall, and when controlling for certain factors, reduced risk of HIV infection by 78 percent.

Also, the introduction of Truvada as PrEP expands screening opportunities, when individuals

are required to be tested for HIV before beginning treatment. We are longstanding advocates of increased testing and recognize its critical role in effective HIV prevention, care, and treatment. With 20 percent of HIV-positive individuals unaware of their infection, driving 50 percent of new infections, additional testing opportunities are critical to controlling the epidemic.

Further, PrEP offers a self-controlled intervention that does not require partner negotiation, which is especially important for marginalized populations who may lack access to other forms of self-initiated interventions.

As with any pharmaceutical, there are risks and benefits to PrEP, and decisions to begin the drug will need to be made by clinicians and patients together. Comprehensive patient education on the importance of adherence and on the risks and limitations of PrEP will be essential, as will supplemental counseling and other ways to promote HIV prevention.

The AIDS Institute believes that these risk

reduction techniques, used simultaneously with PrEP, would further curb HIV transmissions, and that the effectiveness of Truvada as PrEP has been demonstrated by the applicant. We urge the FDA to approve the efficacy supplement for the drug Truvada to include indication for PrEP. Thank you.

DR. FEINBERG: Thank you.

Speaker number 26.

MR. WARREN: Hello. I'm Mitchell Warren. I have the pleasure of directing AVAC, an advocacy organization devoted to health research and health delivery. I also represent a coalition of organizations -- I would argue the largest out there -- of organizations both advocacy and service delivery, committed to doing the right thing and following the evidence. I have no conflict of interest, and AVAC takes no funding from any pharmaceutical company, including from Gilead.

For 17 years, we have been advocates for prevention research. And it is so exciting to stand here in front of you so that we can begin to talk about access to a new prevention option.

At AVAC we have tracked PrEP research since the very beginning of the trials, and our advocacy from day one has been clear: follow the science, follow the evidence. And the evidence leads us here today. And for those of us that have been here this morning to watch the presentations of the data, of the evidence, it is clear.

It is clear that over the past 18 months, this evidence is as exciting as it is complex and challenging. Some argue that the data is mixed, but we believe strongly that the data supports a favorable risk/benefit assessment adequate to approve Truvada for PrEP indication for sexually active men and women, the first question put to all of you on this committee. We recommend that the committee recommend, and FDA approve, that recommendation.

I ask that you not confuse the trial populations in which the studies were conducted with what the evidence actually says. As presented here, as published, and as presented in past conferences, the data is clear. If you perceive

yourself to be at risk of HIV, if you take your pill every day, if that pill is part of a full package, a full intervention, including condoms, counseling, and testing both before initiating PrEP and while on PrEP, you can derive significant protection.

The ifs and the hows are huge and complex, but they are not reasons not to approve this supplemental NDA. Rather, they are exactly why this committee should recommend and the FDA should approve it, because it will allow the FDA, Gilead, health providers, advocates, and patients and future PrEP users the chance to focus, to focus on a label, to focus on evidence-based educational materials, and to focus on a REMS that will support safe and effective use.

In fact, approval is the best way to manage the many issues you've heard raised here. They are not reasons not to do it; they are reasons to do it, because the implementation studies, the demonstration projects, the postmarketing studies, are exactly the way to reduce the concerns of

potential condom migration, of potential resistance, of potential poor adherence.

This is the time to add another prevention method to our approach to end this epidemic. I ask you to please approve it and address these issues to make sure that safe and effective use can be part of our package.

DR. FEINBERG: Thank you.

Speaker number 27.

MR. FRANCIS: Yes. Good afternoon. My name is William Francis. I'm the executive director for Citywide Project out of Atlanta, Georgia. Atlanta is currently number 6 in the country for new cases of HIV and AIDS, largely within the African American MSM community as well as African American heterosexual women. The population that I serve personally each day are the hardest hit throughout the Southeast.

As the executive director, I sit on several boards and I work with several coalitions, collaborate with several organizations locally and nationally, and work very diligently each day to

see the end of AIDS. So there would be nothing more I would rather do than to stand here before you all today and say I support PrEP. But in all that I do and all that I serve, I can't.

As a professional working in both the prevention and testing side, as well as on the linkage to care and treatment side for the last three years, I think I spend more time reeducating on HIV, trying to lessen the stigma around being positive, and the stigma associated with even getting tested, and, sadly, even discrimination and criminalization issues that many still face.

Like so many others, I was excited to hear about the prospects of a new prevention tool, even more excited when the CDC promoted PrEP to be used in a prevention arsenal. But after I read a little bit more and did my own due diligence, I realized very quickly that PrEP wasn't and isn't the it. We are all talking about a new tool in a prevention box. But yes, you can drive a screw through a board using a hammer, but that doesn't make it the right tool, and it will cause damage to the board.

So with the time I have allowed remaining, I want to just ask you not to focus on the data but funds on the human factor behind the human immunodeficiency virus. I recently did a speaking tour throughout the Southeast, and I talked to many different people in Virginia, Tennessee, North Carolina, South Carolina, Georgia, Louisiana, and Alabama. The magic pill, the cure, wasn't what people thought it would be.

A young MSM thought he wouldn't need to use condoms any more. He wouldn't have to live with the fear of contracting HIV, and didn't even realize that STDs aren't prevented by the other blue pill.

I spoke to a mother of three that figured that it would work for her, and sadly, I had to tell her that the trials were stopped because they weren't as effective in women.

Another person that thought it was a cure was a little dismayed and somewhat baffled because his circle thought it would be. And the there was the grandmother, the daughter, and the son, all

positive, that thought that this thing, this PrEP, would prevent the next generation, from getting HIV.

Even a colleague that was dumbfounded when I spoke about the side effects, cost, adherence, and resistance, he too was initially in full support simply because of what he heard in an HIV planning group meeting, he said, where they were already promoting PrEP as the next best thing in prevention.

All I can say is that although I myself am HIV-positive, I am scared of what PrEP would do in the communities that I serve. Thank you for your time.

DR. FEINBERG: Thank you.

Speaker number 28, please.

MS. MCLENDON: Good afternoon. I have no conflict of interest. I'm Elizabeth McLendon. I live in Columbia, South Carolina.

In 1978, I moved to San Francisco, just before the HIV/AIDS epidemic hit us. I stayed there until 1999. In those early days, I lost over

200 friends and acquaintances to HIV. Even now I have too many friends living with this virus and struggling both with staying adherent with the medications and battling the debilitating stigma and ignorance.

The phone numbers of several of my friends who lost the battle with AIDS in recent years are still in this phone. I cannot delete their numbers, and I work in their honor.

Since moving home to South Carolina, I have been working and volunteering in the HIV field. A few of those positions have been as director of the ecumenical AIDS ministry of the South Carolina Christian Action Council, Ryan White program manager of the Columbia oral health clinic, and coordinator for special projects and volunteers at the South Carolina HIV/AIDS Council.

My concern with PrEP is that people will not take it every day and the damage that will cause. In a perfect world, where every single person in the United States who is already infected knows she or he has the virus and is in care and receiving

medications, PrEP would be an interesting experiment.

We do not live in a perfect world. For years now, South Carolina has had a waiting list for people who know their HIV-positive status but cannot receive the lifesaving drugs. At times, that list has had over 900 people on it.

When HIV-positive people cannot get drugs that will save their lives and reduce their infectiousness by 96 percent, how can we instead give the very same drugs to people who do not have the virus? Where in the common sense in that?

To prevent HIV infections, we already know what to do, get those already infected on treatment, decrease the number of sexual partners, and use condoms. If the intended recipients of PrEP are not able to keep the number of their sexual partners to a minimum or to consistently use condoms, why on earth do we think they would be able to take a pill every day at the same time for years on end? All my experience working in this field and my observance of human nature tells me

this will not happen.

This is especially true given Truvada's common and unpleasant side effects like diarrhea. To be blunt, this past Friday at an outdoor HIV event in South Carolina, one of my volunteers, whose HIV medication causes diarrhea, had just such an explosion of uncontrolled diarrhea that sent her running to a convenience store bathroom. She vainly tried to clean herself and her clothes with just a sink and paper towels. This young woman was utterly mortified. Her HIV drug? Truvada.

I don't believe -- actually, what is the likelihood that PrEP participants who are not sick will endure more than one such embarrassing and messy episode? Thank you.

DR. FEINBERG: Thank you.

Speaker number 29 is not here, so we'll move on to speaker number 30, please.

MR. GUILLEN: Hello. My name is Salvador Guillen. I'm a Latino, gay, HIV-negative man. I'm one of the lucky ones that got safe sex education at home. I learned the importance of protecting my

health and using condoms.

Latinos on the United States continue to be heavily impacted by HIV and AIDS. Studies have shown that Latinos with HIV/AIDS may face additional barriers to accessing care. I have been in an HIV field for 15 years. I have been an HIV testing counselor, a volunteer coordinator. I've been in HIV marketing and advocacy, and at times, a counselor for people -- for my family and friends about HIV.

I'm currently in an eight-year relationship. I'm a serodiscordant couple. My partner is HIV-positive. I have seen him go through the challenges of managing HIV, including the side effects of the drug he is taking; the nausea, the vomiting, diarrhea, anemia, depression, fatigue, have been challenges that we have faced together. Long-term side effects including heart disease, potential liver damage, and of course the constant doctor visits have been challenges -- I'm sorry.

I could go on and on, but my time is limited. Managing HIV is not as easy as people

think. Dealing with the daily drug cocktails and its side effects are part of our daily life. An HIV-positive person may look healthy on medication, but its challenges affect our daily life, the challenges that most people don't see. I don't understand why anybody would decide to take this difficulty and side effects if they're not HIV-positive.

I must say that at first, when I've heard about PrEP, I got a little excited. But the more -- I'm sorry. I must say, when I first heard about PrEP, I got a little excited and I thought, maybe in my relationship we don't have to use condoms. But the more research I did about the studies that were conducted, the more disappointed I got.

I wish that Truvada was the magic pill, but I don't think it is yet. If PrEP is approved, I truly believe that it's going to lead to more infections. So I ask you here to please look at the evidence and look at the real world situation, and make the right decision.

DR. FEINBERG: Thank you.

Speaker number 31, please. Is it possible to move the timer thing a little bit to the left? It's very hard -- thank you. Because it's hard to see through that gentleman's forehead.

(Laughter.)

MS. HUDSON: Good afternoon. My name is Fannie Hudson. I'm a registered nurse specializing in HIV care. I have been involved in this field for nine years providing care in North Florida. As an advocate, caregiver, and friend of people with HIV, it is my belief that more studies need to be done before we make Truvada for PrEP generally available.

In my community, approval of Truvada as PrEP, it's like saying, here. Take this magic pill. You won't get HIV. Despite what has been said about PrEP, this is what the people in my community will hear. As a result, it will make it even harder for people, especially women, to protect themselves.

One example that I can share is after taking

a cultural competency class, I have been able to look at the spread of HIV virus differently. The class was taught by a professor from the South Florida University of Tampa. She spoke about going to Mexico and living there and doing HIV prevention.

Forming a relationship with one of the women, she learned, in this particular community, women already were educated about the spread and knew about HIV prevention. But they were getting the viruses from their husbands and lovers who were living and working in the United States and would come back home for a period of time.

The situation was this. Customs were that male dominance or submissiveness determined who could or would spread HIV. To make her husband wear a condom could mean that you did not trust your husband who you were financially dependent upon, which means women could not and did not insist on condom use.

After this class, I took a look at my own culture in the African American community. And

there is an unspoken language, but the message is the same. If you love me, you will not make me take PrEP or you won't make me wear a condom. This is how the viruses continue to be spread. And I would ask you to please take another look at it and see if the virus is going to win over PrEP or PrEP is going to win over the virus. We would like to actually know that we would stop the spread of HIV and AIDS. Thank you very much.

DR. FEINBERG: Thank you.

Speaker number 32, please.

MS. PINTER: Hi. Good afternoon. My name is Amy Pinter. I don't have any financial relationships to disclose. I'm a registered nurse living in Florida, and I've worked in the HIV field for the past 12 years.

When considering the efficacy of a drug, it is incumbent upon this panel to take the world as it is, not as we wish it could be. It is useless to consider the efficacy of a drug used under conditions prescribed, recommended, or suggested by a manufacturer if those conditions are flatly at

odds with the world as it is.

Such is the case with Truvada as PrEP. For PrEP to have any effect, adherence in the form of daily dosing is the linchpin of this regimen. If people don't take the drug daily, they will not acquire whatever preventive effect it has to offer. However, the iPrEx study upon which this application relies establishes what is already common knowledge for most disease states: Adherence to medication regimens is extremely haphazard.

The iPrEx trial showed that Truvada use correlated with only a 44 percent reduction in HIV infection. One of the primary reasons for this dismal outcome is that in this and other studies, many people did not take the drug daily.

For example, the iPrEx study found that among 34 subjects who had contracted HIV while taking Truvada during the study, Truvada was only detected in lab analysis of three of those patients. It logically follows that even with all of the adherence and prevention measures contained

in the study, including being paid to participate, adherence, counseling, and pill counts, only 3 of 34 subjects were actually taking the study drug with any regularity.

Overall, approximately 46 percent of all participants in the Truvada arm of the iPrEx study were found to have no detectable level of the drug in their blood, meaning they were not adherent and were not taking the drug as indicated.

This lack of adherence to a medication regimen is not unusual, and indeed is consistent with nonadherence rates in many disease states, such as with statin use and oral diabetes medications. However, it does confirm that large numbers of people will not take Truvada as indicated for PrEP.

As a nurse, one of my biggest challenges is keeping HIV-positive people who are sick and have every incentive to take these life-saving drugs adherent to their medication regimens. It will be even harder to keep people who are not sick and have no disease adherent.

Of course, under real world conditions, the vast majority of candidates for PrEP will not have access to this array of supporting services, and none will be compensated. In fact, the high cost of the drug may make adherence even more difficult.

At a minimum, the data does not establish that Truvada for PrEP will be used as indicated and therefore will not be effective. This intervention needs much more study before substantial evidence of its effectiveness is found. Thank you.

DR. FEINBERG: Thank you very much.

Speaker number 33, please.

DR. COLON: Hello. Thank you for giving me the opportunity to speak to you today. My name is Rebecca Colon. I am a physician, board-certified in family medicine and credentialed as an HIV specialist by the American Academy of HIV Medicine. I have been practicing HIV medicine and primary case for primarily the MSM community for approximately six years in Fort Lauderdale, Florida, where approximately 60 percent of my patients are HIV-positive and 40 percent are HIV-

negative.

I do have something to disclose. I am on Gilead's speaker bureau. And though I am, I am here to express my concerns regarding PrEP.

Approximately one year ago, patients began asking about pre-exposure prophylaxis. One patient comes to mind that was very interested in PrEP. He expressed that he had what we call condom fatigue and was looking for a possible alternative to condom use.

So I reviewed the data with him from iPrEx: the concern of only a 44 percent efficacy in preventing infection, when condoms are 95 percent effective in preventing the spread of HIV. The fact that the medication is required to be taken every day to be most effective; and that there are the potential for gastrointestinal and kidney problems associated with the medication were reviewed with him.

I asked the patient if he thought he could take a pill every day; and if he did, would he continue to use condoms? He stated that he

wouldn't use condoms if he took the pill because the point of taking it for him is to have an alternative to condoms. He also expressed concerns about having to take a pill every day and possibly still get infected. This scenario led me to two very serious concerns about PrEP.

This particular patient was very candid with me about his thoughts and behaviors, where most patients aren't this open and decisive. He did bring light to the fact that with the possible protection of PrEP, condom use would cease for him. Individuals like him may think that they are protected by PrEP and possibly engage in more risky behavior. There would be a decrease in condom use because if individuals feel they are protected by another measure, they will not continue to use them on a consistent basis.

Secondly, the efficacy data was not very impressive if doses were missed. It is difficult enough to get patients to adhere and to buy into their treatment regimen for HIV when they're HIV-positive and need the medication. Individuals who

don't necessarily need the medication are likely to be less adherent.

The iPrEx study is a perfect example of poor adherence, and this was in a study setting where the subjects were compensated and given extensive prevention counseling that doesn't exist in the real world.

In closing, due to the strong likelihood of decreased condom use and poor adherence, I do not support PrEP at this time. We need to promote testing and treating those that are found to be positive, and education. Thank you.

DR. FEINBERG: Thank you.

Speaker number 34, please.

MR. ENGERAN-CORDOVA: Good afternoon, committee members. My name is Whitney Engeran-Cordova. I'm senior director of public health at AIDS Healthcare Foundation.

My primary professional responsibility is to run programs to help people know their status, help them link into care, and try to prevent people from acquiring HIV in the first place. I have no

conflict or relationship with Gilead Sciences.

Using this treatment as a preventive measure for HIV will be seen as a medical condom. It is a shield that will allow people to have unsafe sex. This is not hyperbole; it's common sense.

At one PrEP forum I attended at UCLA several months ago, one participant, a gay man, came up during a break and asked me, "When are we going to be able to have fun again?" I understand his feelings, particularly as a gay man who became sexually active in the early '90s. It was scary then, and it still is now The impulse to find something to alleviate this fear is palpable and it's real. The risk compensation that will occur with the availability of this medication is evident.

I would ask you to use common sense regarding what you know and what you have seen with your patients and clients, and what you think will happen if people are taking a pill they believe will prevent HIV infection. There is no quick fix. There's no solution that absolves us from the fear

of becoming HIV-positive, nor the responsibility of negotiating safe sex with partners. One of the questions you have as a committee is about making this an indication only for MSMs.

The idea that you would suggest that only sexually active HIV-negative men who have sex with men should take a pill every day in perpetuity is frightening -- people who do not have a disease on a drug for decades. So if we want to control HIV and you are gay, take a pill, see your doctor, and you're safe.

You will fill in the blanks on the headlines. You fill in the blanks on those headlines, and you fill in the blanks on what this says to young gay men, if this is just an indication for men who have sex with men.

I urge you in the strongest possible terms to be mindful of not just what the drug does, but the effects of the availability on this treatment that it would have on our communities. If you find the science indicates effectiveness, I suggest to you that the way it is used has not been

sufficiently explored. It's not ready yet. On the other hand, finding those who are infected with HIV and getting them into care carries none of these problems. Let's not act too hastily. Thank you.

DR. FEINBERG: Thank you.

Speaker number 35, please.

MR. COLLINS: My name is Chris Collins, and I'm vice president and director of public policy at amfAR, the Foundation for AIDS Research. amfAR is dedicated to ending the global AIDS epidemic through innovative research. I have no financial conflicts.

FDA's memorandum that you have in front of you observes the sustained seriousness of the AIDS epidemic in the United States, its heavy burden in particular communities, including gay men and African American men and women and others. It observes what it calls the variable effectiveness of current HIV prevention interventions. That memo and today's presentations detail clinical studies that have provided strong safety and efficacy data on Truvada as PrEP.

So today the question is, given the epidemic we have and the clinical data at hand, what is the logical next step with this product?

We believe that while we continue clinical research, it makes sense to begin to learn more about PrEP use in the real world through provider and consumer education, postmarketing research, and demonstration projects. Based on the information available to us, we strongly support moving forward with an indication for Truvada as PrEP, and we believe there are compelling reasons to include all three of the groups in your question number 1 in that indication.

It's important to remember that in the U.S. epidemic, the risks one takes are not well-correlated with one's vulnerability to infection. The truth is, we're all human, and humans sometimes slip and don't use protection. And for many people in higher-risk communities, if they slip just once in this epidemic, their chances of becoming infected are elevated. So we need new tools to fight this epidemic, new tools that are used as

part of a comprehensive approach that includes treatment, condoms, and education.

The research has brought us to a point where the decision about whether or not to use PrEP should be between a doctor and a potential consumer. I don't think we want to be limiting access to a safe and effective product based on our assumptions and conjecture about the behavior of some.

As an HIV-negative gay man, I can tell you I'm pretty good at taking my medications. And I can also tell you that if the FDA just assumed I wasn't, I wouldn't be very happy about it.

Now, it's true the ultimate public health impact of PrEP is not yet known. PrEP is certainly not for everyone. But it may have a role in bringing overall HIV incidence down, particularly if used in a targeted way among groups of elevated risk.

I hope the REMS strategy will tailor communications and services to a diversity of providers. We must make sure the communications

and services are suitable for young gay men, including young black gay men, and women of color, and their providers.

In sum, it's time to learn how PrEP may be useful in the real world. The next step in pursuing answers to these questions is an indication from FDA. Thank you.

DR. FEINBERG: Thank you.

Speaker number 36 isn't here, so we'll move on to speaker number 37.

MS. RUTHERFORD: My name is Monica Rutherford, and I have no financial conflict. I have been a nurse for 35 years and nationally certified in HIV as an ACRN, AIDS-Certified Registered Nurse, working in a disease management program, exclusively for patients who are HIV-positive, for the past 12 years.

I also have experience working with HIV providers in Ukraine, Russia, and South Africa. And I am an active member of the Association of Nurses in AIDS Care, having served as secretary, president-elect, president, and presidential

advisor.

Always foremost in any discussion regarding HIV treatment are the topics of side effects, adherence, and resistance. Unlike most medication taken to make you feel better, HIV medicine doesn't provide this outcome. In fact, it can make you feel worse, producing side effects including nausea, vomiting, diarrhea, neuropathy and muscle pain, osteopenia, and hepatotoxicity, which I saw personally in many of my patients.

I'll never forget a patient I saw in Africa, walking into the clinic on his hands due to his severe neuropathy caused by HIV medication. I have also had several patients who had to be removed from this medication due to the kidney damage it can cause.

When I go into a patient's home, I ask to see all their pills so I can determine how effectively they're taking their prescribed medications. Many times my patients will bring out a large box full of unused prescription medications for their HIV and other comorbid conditions.

Reasons for nonadherence range from complaints of side effects to changes of orders secondary to poor kidney function caused by the medication, and the simple but most frequent, "I forget."

HIV is a smart virus and easily forms mutations that prevent antiretroviral medication from working. Studies show that at least 95 percent adherence to HIV medication is necessary to provide protection from resistance. Truvada is taken once a day, so in a month's time, only one dose of medication could be missed without risking the development of mutations and resistance.

In the population of patients I see, I can assure you this is a difficult goal, and these are people who know they're positive. Can we realistically expect a negative person to be more adherent?

We also know that medications can be shared. I had a patient confide to me that her husband wouldn't come for treatment himself because of stigma, so she came and shared her medication with him. Knowing this happens with diagnosed patients,

we logistically expect it even more in negative population, leading to more resistance.

Prevention of HIV is a noble goal, but let's be realistic. Truvada is an important medication in our arsenal to fight HIV. Thank you.

DR. FEINBERG: Thank you.

Speaker number 38.

MR. BROOKS: My name is Douglas Brooks. I'm senior vice president at Justice Resource Institute in Boston. I've served as consultant to pharmaceutical companies, including Gilead Sciences, but I have no financial interest in the outcome of this meeting.

JRI is a 40-year old, 1600-employee human services agent, serving patients and clients throughout Massachusetts, Rhode Island, Connecticut, and Pennsylvania. JRI's view is that Gilead Sciences' application for Truvada as PrEP indication should be approved, and will serve as an essential component of the comprehensive biopsychosocial interventions that are necessary for populations at high risk of HIV infection,

including the thousands of young men who have sex with men whom we've served through our primary care and behavioral health services, and through our HIV, STD, and viral hepatitis testing and prevention services.

PrEP would also provide the same prevention options for the partners of the clients, the hundreds of clients we serve through our housing programs for people living with HIV.

JRI believes that the efficacy of PrEP, ranging from 73 to over 90 percent for those who adhered to the regimen and had detectable drugs in their system in clinical trials is significant. The overall benefit in relation to known risk is at an acceptable level, and that any safety risk can be mitigated with proper labeling and educational materials.

We do believe that education programs should go beyond patients and prescribers, and that the development of education materials for nonmedical personnel such as social workers, behavioral interventionists, and case managers would be

appropriate.

The background package for this meeting notes the disparities in HIV incidence among young black MSM. Greg Millett and others have demonstrated in research that these disparities persist, even though these men do not engage in riskier behaviors than others. Many believe that this is because they tend to engage in sexual activity within their own communities. Higher community viral loads place them at greater risk for HIV infection.

JRI and our membership organization, the National Black Gay Men's Advocacy Coalition, believe that PrEP will provide an additive protective component to the testing and condom prevention package that can help end this tragic situation.

There's been much discussion about risk compensation and poor adherence. At JRI, we've learned that with proper primary care, education, and psychosocial supports, and a focus on their resilience, not their deficits, our patients and

clients are capable of making healthy decisions for their own lives.

As a licensed clinical social worker who spent 20 years working directly with gay men of all colors and overseeing programs that serve them, I know that they don't require our paternalizing them. Drawing from social work's profession of dignity and worth of the individual, we must treat patients with respect, promote socially responsible self-determination, and enhance their capacity and opportunity to change and address their own needs.

Approving this application would be in keeping with that principle. Our country needs to expand, not restrict, our prevention portfolio.

DR. FEINBERG: Thank you.

Speaker number 39, please.

MS. UFOMATA: Good afternoon. My name is Omonigho Ufomata, and I have no financial conflict. I am speaking as a health policy professional, with almost 10 years' experience working in Congress and city government, and as a concerned DC resident.

In my analysis, the research shows that

Truvada is not an effective prevention tool as PrEP, for several reasons. The dangerous side effects, the adherence challenges, the complications with drug resistance, the exorbitant cost of Truvada, and the minimal efficacy of the PrEP studies already conducted raise serious concerns.

Most importantly, it is my view that an FDA approval of this medication as PrEP will send a dangerous message to young people. We do not want to convey a message that a drug which has shown only mineral effectiveness, even under best case and controls scenarios, is a reliable tool to prevent the spread of HIV when other methods are 95 percent effective and available widely.

Case in point, Washington, DC, which has some of the highest HIV infection rates in any city in the United States and in the world. Previously I worked as a senior health policy advisor in the executive office of the Mayor. In my experience, the message health and policy professionals work to communicate to the public is that prevention is key

to controlling the spread of HIV, and that condoms, when used properly, are more than 95 percent effective.

I participated in the studies to measure the attitudes of young people towards prevention and sexual health. We found that there were already confusing attitudes towards safe sex and what tools are most effective as protection against the transmission of HIV.

The availability of PrEP, a much less effective mode of protection, would create a more confusing message and encourage risky behavior. It would be a tragedy if our residents choose to use PrEP instead of condoms after all that has been done to promote their use.

The FDA has a direct responsibility to protect the public health and consumer safety. The PrEP studies to date simply do not show that this drug is safe enough to be made available to the wider public.

In conclusion, those of us who are fighting the spread of HIV are in a race against time. The

availability of Truvada as PrEP will create confusion, encourage risky behavior, and fail to provide adequate protection. I urge you to conclude that Truvada is not ready for HIV prevention use in the general public. Thank you.

DR. FEINBERG: Thank you.

Speaker number 40, please.

MS. MAYERS: Hi. My name is Joanne Mayers, and I have been a registered nurse for over 12 years, working with the HIV population in Central Florida. I have no financial obligation, nor am I receiving any monetary compensation at this time for presenting here today.

With my experience in the field, I would just like to shed some light on the deficiency in the PrEP therapy. Number one, claimed adherence has been and always will be a problem. For example, a 31-year-old female diagnosed in 1999, who started with a CD4 count of 300 and a viral load greater than 10,000, was started on ARVS, however, after feeling better and the viral load becoming undetectable, stopped her therapy.

Today she returns with a CD4 count of 178 and a viral load greater than 100,000. She is consistently missing at least one to two doses weekly. This client is infected with the HIV/AIDS virus, and adherence is still a main problem. Taking her medication daily is vital not only to her survival but to her quality of life, but she still has difficulty maintaining her adherence.

Two, with the false hope of protection offered by PrEP, risky behavior in individuals will increase. While the use of condoms is already proven 95 percent effective in the transmission of the virus, PrEP only cuts that risk to 44 percent. An increase in risky behavior may potentially cause a pandemic in the increased rate of infection and other sexually transmitted diseases.

Three, researchers found a significant risk of kidney disease and damage from Truvada. Subsequently, a 21-year-old male infected prenatally with HIV is now on renal failure dialysis three times weekly. He is now totally dependent on social security for his medical

insurance. Although he appreciates being among the living, he would trade his dialysis treatments for a part-time job. Truvada increases the risk of kidney failure, or with this client the kidney failure may have been contributive to this.

In looking at just these few factors, the conclusion is clear. The use of condoms is practically free and does not in any way contribute to kidney failure. The use each of condoms has already proven to be effective in decreasing transmission of HIV and the AIDS virus.

Adherence for clients infected with the virus is a problematic situation in many cases. How, then, can we expect individuals who are not infected to completely understand the importance of 100 percent medication adherence? We need more evidence before we can make a final decision. Let's continue to educate the population on the measures that do no harm and have already been proven effective. Thank you.

DR. FEINBERG: Thank you.

We'll move on now to speaker number 41.

MR. WEINSTEIN: Good afternoon. My name is Michael Weinstein. I am the president of the of the AIDS Healthcare Foundation. AIDS Healthcare Foundation is the largest AIDS organization in the world, and we are currently caring for more than 169,000 patients worldwide. AIDS Healthcare Foundation gets larger and larger the more people become infected, and we don't want to see one new infection.

I dispensed with my prepared remarks, and I want to talk on a common-sense basis. There is no reason for a person to take this medication if they use condoms, and there's no reason to use condoms if they take this medication.

So the assumption, based in the iPrEx study, that there was no risk compensation is false because it was self-reported. The very same people said they were taking the medication, but half of them did not.

Condom use is being denigrated. Condom use is highly successful. Only 50,000 new infections per year from 1.2 million people; if no one was

using condoms, that number would be far higher. Only 28 percent of the people in this country have their virus under control, according to the CDC.

You want to look at an example of the success of condoms? Look at me. I'm 59 years old. I was living in New York City when this broke out. Condoms have protected me. So if you want to do no harm, don't reduce the use of condoms. I'm old enough to remember when people took penicillin before a night on the town in the '70s. That ended badly. This is not primarily a pharmacological issue. It is primarily a sociological issue. Will it work in the real world? And the answer is no.

One of the areas that's so inadequate in the iPrEx study, aside from the fact that most of the people studied were outside the United States, only 10 percent of the recipients were black. Yet 50 percent of people living with HIV in the country are black. How can that be adequate?

Let me say, then, as I'm running out of time, a wallet card? Really? A wallet card instead of testing? That is so outrageous. This

is going to be a free-for-all -- no testing required, no counseling required, no database, no follow-up. Approving PrEP without testing would be a reckless act. It would be a new Tuskegee experiment.

DR. FEINBERG: Thank you.

Speaker number 42, please.

DR. RODWICK: Hi. My name is Barry Rodwick, and I appreciate the opportunity of my three minutes before this committee. I am a physician in Florida. I have been in practice with seeing primarily HIV and AIDS patients for the past 20 years. I currently have about 900 active patients.

Over the years, I've gone from a practice providing mostly palliative care to one where I am now managing a chronic disease. And I'm also managing the coexisting illnesses of aging and, of course, managing the toxicities of the very antivirals that have kept these patients alive for so long. I have several concerns about the proposed use of Truvada for pre-exposure prophylaxis, but I will only address one of these

at this time.

Tenofovir is not as benign a medication as it was thought to be when it was first approved. And the more experience that I've had with it, the more concerns that I have developed, one being renal toxicity.

There is a recent pivotal study detailing the long-term consequences of tenofovir which has just been released. Researchers at the Veterans Administration and the University of California studies over 10,000 patients during a time period covering 10 years or more. Of course, this is way more patients that have been in the studies that the FDA has received for approving Truvada for PrEP, and these patients in this study have been studied for a much longer period of time.

The researchers concluded that after following these patients for 10 years, the risk of protein in the urine indicating kidney damage rises 34 percent for each year on therapy. The risk of developing chronic kidney disease rises 33 percent for each year on therapy. The risk of a rapid

decline in kidney function rises 11 percent for each year on therapy.

This represents year over year increases. The patients in the studies, including iPrEx, were not followed for a very lung period of time. Each year the person takes tenofovir, the risks rise by these amounts. And the researchers also found that by discontinuing tenofovir, the elevated creatinine levels and kidney damage did not return to normal.

These experiences have also been demonstrated in my practice, where we see elevated creatinine levels, and we do not see them return completely to normal once tenofovir is stopped. We even have patients that temporarily have to go on hemodialysis.

I realize that our goals are to stop the spread of HIV and break the chain of infection, but I'm not convinced that Truvada used in this capacity in the long run will help us reach that goal. Thank you.

DR. FEINBERG: Thank you.

Speaker number 43, please.

MS. KOOIMAN: Good afternoon. My name is Bettina Kooiman. I work in Florida. I started my nursing career 20 years ago in the Netherlands. My primary patients are HIV-positive. Even in those few studies that found a correlation between PrEP and reduced infection, that efficacy was low, both in absolute terms and relative to other HIV prevention methods such as condom use, found to be 95 percent effective, and providing treatment to people who are HIV-positive, found to be 96 percent effective in preventing HIV transmission. Even these poor findings will not be replicated in the real world. The cornerstone of Truvada having any possible efficacy as PrEP is medication adherence.

As shown in a 2011 study, medication adherence in general is higher in clinical studies than results found outside clinical studies. That is the real world. This is due for a number of reasons. First, participants in the clinical trial are more involved with their conditions and their treatments than the general population, and thus are more likely to be adherent. The second and

most important reason is the perhaps necessary artificial environment of a study.

In each of the PrEP studies, participants received regular, in some studies, monthly medical exams; regular, in some studies, monthly risk reduction counseling for HIV and other sexually transmitted infections; regular, in some studies, monthly HIV testing; regular free supply of male and female condoms; regular, in some studies, monthly medication adherence counseling, including pill counts; free supply of drugs.

In the real world, Truvada retails in excess of $13,000 a year. Even with insurance, most will have to pay copays. There was compensation for participating in the trials. People literally were paid to take these pills.

Despite all of these interventions, all of which were aimed expressly at medication adherence and risk reduction, virtually none of which are available outside a study environment and which are much more rigorous than the proposed risk evaluation and mitigation strategy, the iPrEx study

still found efficacy of only 44 percent. This result will not be achieved outside a trial.

Given the 95 and 96 percent existing efficacies of other prevention interventions, the less than 44 percent efficacy that will be observed is not sufficient to establish Truvada as PrEP.

(Microphone turned off.)

DR. FEINBERG: Thank you.

The open public hearing of this meeting, this portion, has now concluded. We will no longer take comments from our audience.

I think this is a good time to take a brief break. It's 10 to 4:00. If everyone will please come back at 4:00, we will resume with questions.

(Whereupon, a brief recess was taken.)

Clarifying Questions from the Committee

DR. FEINBERG: Okay, everybody. It's a couple of minutes after 4:00, so we're going to get started.

Panel, this time if you just raise your hands, we'll take you in order. And let me -- come on in, folks -- and this segment will be for

clarifying questions. So let me clarify that again.

This is to ask specific questions about the presentations that we heard from the sponsor, from the FDA, and I should also mention Dr. Paxton from the CDC. If you have specific questions for her presentation of the CDC studies, let's try to get those questions in early because I understand she has to leave at 5:00.

Let's do this, and then we will move into the more substantive discussion and cross-discussion that we need to have. So right now we're really trying to get our facts straight.

Okay. Who's up?

DR. MURATA: Yoshi Murata from the University of Rochester. I have a question for the sponsors. In either of the studies, were there any estimates from seroconversion till diagnosis of that seroconversion and cessation of the PrEP regimen to the formal treatment regimen?

I understand that this may be limited, but that the full answer may be at the timing of every

scheduled serological screening. But if there are any estimates to how long the patients were unknowingly on the PrEP regimen while an acute seroconversion event would have occurred, then that might be of interest.

DR. CHENG: Thank you for the question. I'll ask Drs. Grant and Baeten to come speak to the duration of time in between the time when seroconversion may have occurred and the next study visit.

DR. BAETEN: Thank you for the question. In Partners PrEP, the majority of infections were detected within three months of seroconversion, approximately. We measured HIV RNA on back-testing on samples that were collected every three months; for less than 50 percent of individuals were they RNA-positive prior to the month at which seroconversion was detected. So for the vast majority of individuals, it was within a three-month period.

DR. GRANT: Slide up, please. For the iPrEx study, the majority of diagnoses of HIV infection

were made at the time that the person was antibody-positive and also RNA-positive at the same visit. However, there were 15 percent of seroconversions that would have been detectable on an RNA assay at some time -- at some previous visit. Typically, this is the visit 4 weeks prior to the first antibody-positive visit.

So the majority of diagnoses were made at a time when both antibody and RNA tests were positive.

DR. HUNSICKER: Yes. I have two questions, if I might, first for the -- well, they're actually both of them for the two PIs. But this relates to the question of the explanation for the 42 percent as opposed to 90-some-odd percent protection, which has been attributed to lack of compliance to the study medicine.

Now, I want to say that I find that is reasonably persuasive on the face. However, it is very possible that there is a strong correlation between compliance with the pill-taking and compliance with all the other aspects of sexual

safety.

It would be informative, therefore -- and you actually somewhat addressed -- the first, the iPrEx study, somewhat addressed this. But if you compare the groups in your case control study of the treated patients who did and did not have detectable levels or reasonable levels of the medicine, was there a difference in, for instance, the frequency of other sexually acquired diseases that might suggest that actually, the two groups were imbalanced with respect to compliance with other aspects of prevention?

DR. CHENG: I'll ask Dr. Grant to come speak to that.

DR. GRANT: So it's a very important consideration that confounding can occur in an analysis within the active arm of the study. And importantly, when we looked at HIV incidence in the group that does not have drug detected in the active arm, we see an incidence that is comparable to the placebo arm or a little bit less.

DR. HUNSICKER: Sure.

DR. GRANT: So that actually is an important parameter. That indicates that the relationship between protection and drug detection is not driven by confounding because in the absence of drug detection, we see an incidence rate that is no higher than the placebo.

DR. HUNSICKER: It is possible that there are two offsetting effects. And I'm not saying I think this is likely, but I think it would nail it down if you were to find that, for instance, the frequency of sexually acquired diseases other than AIDS was parallel; i.e., the evidence for protection against other things, using --

DR. GRANT: So we can bring this slide up. This again is the syphilis slide that I showed earlier that showed declining incidence of new RPR-positive syphilis cases.

DR. HUNSICKER: That's placebo versus treated. I'm interested in treated with or without detectable levels.

DR. GRANT: Okay. I understand the question now.

Do we have an analysis of that? No, we don't. So we don't have an analysis of that. But the confounding -- yes. The confounding has been addressed with the --

DR. HUNSICKER: I would just then make the suggestion that it would be worth checking this because if, in fact, there is a similar incidence of other sexual diseases, that would tend to strengthen your belief that it is related to compliance with the medicine.

Does the other person want to say something?

DR. BAETEN: Yes. I think I would have probably three responses to this. The first would be our case cohort analysis was a subset of the study population. And our rate of STIs post-baseline was low enough that I think we would be unable to analyze sexually transmitted infections.

However, our estimate, our 86 and 90 percent protection estimates from the case cohort analysis are identical, once adjusted for frequency of sex and frequency of unprotected sex in the study population. So there appears to be no confounding.

Finally, if I can have one more slide up. This is subgroup analysis for -- this is efficacy, drug versus placebo, for individuals who reported unprotected sex at baseline, which in our study population is a significant risk factor for HIV. As you can see, the placebo arm incidence at the top is 3 and a half percent per year versus less than half that for individuals who reported 100 percent condom use at the time of baseline. And efficacy in the bottom row for the emtricitabine/tenofovir group is equivalent to what it is in the entire study population, 73 and 78 percent, for those who reported no unprotected sex versus those who reported unprotected sex.

DR. HUNSICKER: Okay. I think more informative is that you probably didn't have enough people to make some sensible statement about it. But it's something to consider.

The second question, which is totally distinct, has to do with my being here as a kidney doctor. And I'd just point out that for detection of tubulopathies, looking at GFR and gross total

proteinuria or, more typically, dipstick albuminuria, is probably not the greatest way to go about it.

So I would ask you, when you report proteinuria, are you in fact reporting dipstick proteinuria? And was there any actual estimation of total proteinuria, as you understand dipsticks really only measure albumin?

DR. CHENG: So I'll ask Drs. Baeten and Grant report from their own studies how they would report proteinuria.

DR. BAETEN: Yes. If I could have this slide up, please. The answer to your question is yes. It was dipstick proteinuria only was what was measured in Partners PrEP. This slide demonstrates how we measured and when we measured proteinuria.

We had a trigger for measuring proteinuria and glycosuria only in the context of an abnormal serum phosphorus level. Confirmed abnormal serum phosphorus levels were equivalent across the three study arms, primarily were grade 2, and were rarely associated with 1-plus or greater proteinuria, as

demonstrated in the bottom row, or glycosuria, occurring in 5 percent or less of the study population and equivalent across the three arms.

DR. FEINBERG: Dr. Ellenberg ?

DR. ELLENBERG: Thanks. I'd like to follow up on the first question that Dr. Hunsicker asked about adherence, which is clearly a very important issue here.

We learned a lesson decades ago from a classic study from NIH about how misleading looking at outcomes in adherers and nonadherers can be. And the reason we learned -- the way we learned about it in that study was because they had data on compliance from people who were treated and people on the placebo.

What they found was that the benefits were equally great in those who adhered to the placebo versus those who didn't. And since, clearly, the placebo couldn't have been causing that -- you know, you can say you can't get the benefit unless you take it, but that shouldn't really apply to the placebo -- they adjusted for everything in sight

and reduced it, but still had a huge, huge, effect.

So my question is, do you have any information on compliance in the placebo arm? And can you tell us what happened to infection rate in those who complied with placebo versus those who did not?

DR. CHENG: Dr. Grant?

DR. GRANT: So the prior study that's being cited here, I think, is important because in that study, individuals who were noncompliant with the active arm had a higher incidence of HIV than the placebo arm. And so it becomes important to realize that in iPrEx, that was not the case.

DR. ELLENBERG: I wasn't talking about HIV studies.

DR. GRANT: What's that? It wasn't -- well, it was a vaccine study in which low adherence was -- adherence to the vaccine --

DR. ELLENBERG: This is the cardiovascular study with mortality as the outcome, is the study I'm talking about.

DR. GRANT: Okay. So the point that I'm --

the response I'm making here is, really, that we can look at HIV incidence or outcome of interest in the group in the active arm that did not have detectable drug. And if that's higher than in the placebo arm, it does suggest that there's something about compliance with the intervention that correlates with protection.

In our case, the individuals with active -- with undetectable drug have an HIV incidence that is lower than the placebo arm. So that argues against confounding -- accounting for the association between drug detection and protection from HIV.

DR. ELLENBERG: I don't think it is. What you need is the comparison between the people who complied with placebo versus the people who complied with drug. So I ask again, do you have any data on outcomes in placebo adherers versus placebo non-adherers?

DR. GRANT: Can we have the slides regarding confounding in the analysis of drug detection and HIV risk?

DR. HUNSICKER: Specifically, I would comment that you have said that the history of compliance is not particularly predictive, but the history of noncompliance is predictive. So you could look at whether there is a difference in the frequency -- if acquisition of the disease amongst the people that were self-admitted noncompliant and compliant in the placebo arm. That would do what Dr. Ellenberg is after.

DR. GRANT: Okay. We can bring up this slide. So in this slide, we do see -- this is based on self-reported adherence, which had limited predictive value with respect to drug detection. Adherence was over-reported in the iPrEx trial. But this self-reported parameter of adherence was correlated with drug detection in a rough way.

You can see here that those in the placebo arm on the right-hand side tended to have a lower incidence. But it was a small difference compared to those who reported nonadherence, and the test for trend had a nonsignificant P-value of .78.

However, in the active arm there was a

marked association with adherence to the product, indicating -- or commensurate with its prophylactic activity.

So is this now addressing the question?

DR. ELLENBERG: This gets at what I'm talking about. And what it shows is what I expected. Since overall, there's an effect, I didn't expect the effect to go away. But when you look at the high adherers, it's not the 90 percent that you talked about before; it's somewhat lower. And that's really what I'm trying to get at, is how inflated might that 90 percent be because you're comparing the good adherers on the treatment arm with everybody on the placebo arm. And that's not really a fair comparison.

DR. HUNSICKER: You could, again, go to the non-HIV sexual diseases and see if adherence as reported correlates with that. If it does not -- I mean, it's entirely credible that the pill has a different thing that causes nonadherence than everything else. But it's also conceivable that there's strong correlation, and you could try to

dissect this.

I'm just trying to get a better handle on how convincing the evidence is that this is a 90 percent effective treatment in people who take the drug, as opposed to a 90 percent effective treatment in people who take the drug and do everything else they're supposed to do.

DR. FEINBERG: Dr. Morrato?

DR. MORRATO: I had one question for the sponsors and one question for FDA. So maybe since you're up, I'll ask you first, in terms of the sponsor.

I'm interested in the REMS, and as we heard with many comments in the open public hearing, questions around how does what was done in the trial play out and translate in clinical practice in the real world.

You propose in the REMS, essentially, medication guide, a few pamphlets, and a card. Do you have any evidence that those things will actually ensure the behaviors that you're wishing to see in terms of HIV testing rates, adherence,

compliance, et cetera?

DR. CHENG: I'll Dr. Peschel to come speak to the REMS.

DR. FEINBERG: Introduce yourself, please.

DR. PESCHEL: I'm Tobias Peschel, vice president of drug safety and public health at Gilead Sciences. I'm sorry.

When it comes to the specific risk mitigation strategy around Truvada, I think it is somewhat unusual. And therefore, in regards to your question, do you have any evidence that this REMS will actually do what it's supposed to be doing is difficult to answer.

The reason is that with Truvada and the prevention of HIV, we don't have a situation like we typically do with a REMS, where it's about a specific drug toxicity. But what we are talking about is the question, how can we ensure that a product that has been safely used for 8 years can now be used in a new indication without introducing any barriers to the existing indication?

So this is new territory. And what we have

proposed here -- and slide up, please -- as you can see, it is not just the REMS, but we intend to support the REMS with a variety of additional measures -- can only be start. We have regular REMS assessment reports at an annual frequency, and they will provide the opportunity to actually measure the effectiveness of all of this and then adjust as needed.

DR. MORRATO: Right. If I may add, then, what you provided in the briefing packet is one paragraph on the assessment that basically says you're going to evaluate whether pamphlets were handed out to providers and by providers. So there is no assessment in there that's part of the formal REMS, at least based on the briefing document that we received.

DR. PESCHEL: Can we please see the slide up?

So these are the REMS goals.

And can see as the next slide, please, the REMS assessment?

As you can see here, there are a variety of

data points that are specified in the REMS assessment report. The first three are really around drug usage, the drug used, the number of prescribers using PrEP, the number of prescribers who will have gone through our online training for PrEP.

But then, most importantly, you have the next two, which are the knowledge, attitude, and behavior surveys. Those will be submitted annually to a sample of both prescribers as well as patients. And that assessment will really be an assessment of, has the message, have these key safety risk messages, on the previous slide, reached the prescriber and the patient, and to what extent?

DR. MORRATO: So this a change, then, from what was in our briefing package because this was listed as other studies that you would do but not part of the REMS commitment. Is that correct? Yes.

Since the CDC has had their guidelines out for over a year, is there any data been collected

on how it's being used right now in practice?

DR. PESCHEL: We don't have any firm data on that. So we have no specific data on that question.

DR. MORRATO: Okay. And then maybe either the FDA or you can answer this, and you might have the same data. It relates back to the adherence, and using drug levels as a measure of adherence.

I could not find -- what I'd like to know is what percent of the population would have this sort of intermittent compliance. So in one study, I believe it was called low measurable levels, the way the FDA had it as less than median. In one study, it was sometimes measurable plasma levels.

What is the actual percentage of the population that fell into that? I did my calculations off of the FDA slides, and it looked like about a quarter of the subjects on drug fell into that intermediate range of compliance. And I'm not sure --

DR. CHENG: I think I'll ask the Partners PrEP team as well as the iPrEx team to answer that

question.

DR. BAETEN: Slide up, please. So in Partners PrEP, we measure -- in our case cohort analysis, we have longitudinal samples on individuals on the active arm who did not seroconvert during the study.

This is the distribution at month 1, with the blue on the top being approximately 70, 75 percent of the population having high detectable drug levels; a small proportion in orange, about 5 percent, having midrange detectable levels, somewhat less than suggesting daily dosing, or individual pharmacokinetics; and then approximately 15 to 20 percent on the bottom in green having undetectable levels.

DR. MORRATO: Right. What I'm trying to get at is the overall, not just among seroconverters versus nonseroconverters.

DR. BAETEN: Right. Apologies. So these are randomly selected from the study population and -- next slide -- those individuals who were not taking drug at month 1, most of them continued to

not take drug. And then -- can I have the slide after that, please? Up, please. Great. And individuals who had low levels tended to move up into the high detectable range.

Then the last slide, please, up. And those who had initially high levels tended to stay at the high range. Those drops down into lower ranges are mostly associated with pregnancies and study drug holds that were protocol-required, or missed visits.

So individuals who were taking at the beginning tended to take throughout. Individuals who were not taking at the beginning tended to not take throughout.

DR. MORRATO: Right. So what percent would we estimate, then, would be the percent of people that are intermediate? So if I use the Ns from slide 17 in the FDA slides and slide 24, and I use the Ns that he has in there, I calculated somewhere between 20 and 28 percent were in intermediate.

Is that you would say as well?

DR. BAETEN: That were intermittently using?

DR. MORRATO: Yes. Between the two studies.

DR. BAETEN: I think in part --

DR. MORRATO: Or intermittent levels, or this is --

DR. BAETEN: Right.

DR. MORRATO: Yes. So the ones --

DR. BAETEN: In Partners PrEP, it would be on the -- it would be generally lower than that had intermediate levels, especially if we consider mandatory drug holds for pregnancy, when people did not have access to product, although we still tested their sample in that reporting.

DR. MORRATO: So I guess, then, my last question for the FDA is, do the Ns that you had in your slide take into account drug hold? I think this is Dr. Miele. Yes.

DR. MIELE: I'll ask the clinical pharm people to respond.

DR. WANG: My name is Yaning Wang. If you can show slide -- I don't remember the slide number, the distribution for the --

DR. MORRATO: Slides 17 and 24?

DR. WANG: Yes.

DR. MORRATO: I don't know which -- 17 was the iPrEx and 24 was the Partners PrEP.

DR. WANG: Yes. So for the intermediate, we assumed 28 percent in the 100 random selected population is similar to the overall population. So when you combine this, again, with the positive, which only had like 13 cases, the overall intermediate should be around 29 percent.

DR. MORRATO: Yes. That's what I calculated. So I guess does -- it's important to me because that gives -- you know, you present this notion of this slice, the zone of resistant risk. And what we don't know is how big that slice is, or narrow.

I think to some degree, the understanding of what percentage of the population, even under a very controlled setting is intermittent gives us some sense of that zone of resistance risk. So that's why I want to make sure I'm understanding that proportion properly.

DR. GRANT: So I think that Partners PrEP

has more to say on this very important topic. I can address the issue in iPrEx. Slide up, please.

This is an analysis that was presented by Peter Anderson at the CROI meeting earlier this year. And it represents a collaboration with Albert Liu, who had performed the STRAND study, a crossover study involving directly observed therapy of 2 pills per week, 4 pills per week, and 7 pills per week, yielding levels of drug and peripheral blood mononuclear cells on the left-hand side of the graph. And you can see a dose response.

The levels in the case control study of iPrEx are given on the right-hand side. And in this analysis, only 18 percent of the active arm of iPrEx who remain seronegative had drug levels that were commensurate with daily dosing. Eighty-two percent had drug levels that were commensurate with less than daily dosing. Again, only 44 percent had any drug detection at all.

So in iPrEx, I would say that of the 44 percent that had drug detection, only approximately half had drug levels that were

commensurate with daily use, and the other half of that subgroup had evidence of intermittent dosing.

Again, there was no evidence of drug resistance in any of the seroconverters in the active arm of iPrEx, so despite this intermediate level of drug exposure, we did not see any drug resistance among those who became infected.

These data, taken together, suggest that the slice that John Mellors describes is quite narrow. The concentrations that are sufficient to prevent infection -- excuse me. The concentrations that would be sufficient to select for drug resistance appear to be sufficient to prevent infection entirely, at least in our experience in iPrEx so far.

DR. MELLORS: John Mellors. Just to clarify that, the graphic I showed was a theoretical graphic, with the zone of resistance being a theoretical consideration. But based on the data from iPrEx, Partners PrEP, and TDF2, nobody fit within that zone.

DR. FEINBERG: Before we move to

Dr. Strader, who's next in line, I also found out that Dr Buchbinder needs to leave by about 5:00. So I just would ask the people of the panel, if you have specific questions for Drs. Buchbinder or Paxton, raise your hand now so we can get them out of the way. If not, we thank them for their participation.

DR. WAPLES: One correction. Dr. Paxton, I think, can stay until 6:30. But Dr. Buchbinder is leaving at 5:00 p.m. Thank you.

DR. FEINBERG: Okay. So it doesn't look like anybody has a burning question for either of them. Right? Okay.

So ladies, whenever you're ready to go.

Dr. Strader is next on my list.

DR. STRADER: I have a couple of questions about the Partners PrEP, and then one about the REMS.

How long after starting the medication, on average, did the patients seroconvert to HIV-positive? And was there some demographic? Were they all young? Were they all women?

DR. BAETEN: Can I ask a clarifying question? For individuals who were infected at baseline, or any of the individuals?

DR. STRADER: Yes. Anywhere along there.

DR. BAETEN: Okay. I think if we brought up the cumulative infection curve from the main deck, that would show. Slide up, please.

So these are the post-randomization infections in the cohort, and they occur throughout the duration of follow-up, both infections occurring early after randomization, but also infections continuing to occur between month 12 and month 24, and then few infections after month 24, where we have very limited person-time in the study. So there were infections throughout the duration of follow-up.

Risk factors for HIV infection in the cohort: Women had a higher incidence than men. And if I can bring this slide up, please. So the incidence in women, the post-randomization incidence in women and in men, is in the top of the graphic, right above the table. Women's incidence

in the placebo arm was 2.8 percent per year; men's incidence was 1 and a half percent per year.

Additional risk factors for HIV seroconversion in the cohort were unprotected sex at baseline or unprotected sex during follow-up, and high viral load in the HIV-positive partner.

DR. STRADER: Thank you. And my one REMS question is there was a mention of targeting for prescribers, but I would like to know how that's going to be done since there are no registries for that.

Are you planning to send out information to all primary care physicians, infectious disease specialists, emergency physicians, obstetricians, addiction specialists, or how do you plan to target prescribers of Truvada for PrEP?

DR. CHENG: So the question is how we plan to target, with the REMS, prescribers of PrEP. And I'll ask Dr. Rawlings to come speak to that.

DR. RAWLINGS: I'm Dr. Keith Rawlings. I'm director of medical affairs at Gilead Sciences. Slide up, please.

In the context of -- the easy answer to your question is, yes, we plan on sending out information to all of those individuals. So healthcare --

DR. STRADER: All across the country?

DR. RAWLINGS: Yes.

DR. STRADER: Okay.

DR. RAWLINGS: So the healthcare providers that we are targeting are those who are currently providing care to HIV-positives, physicians, physician assistants, nurse practitioners, all the primary care disciplines that you will see loaded here, OB/GYNs, infectious disease, and addiction medicine.

In addition, we will be sending out and working specifically with locations where individuals who may be at high risk are, independent of the individual specialty, so health departments, community health centers, and public hospitals. We estimate that that would be well over 200,000 individual clinicians in the United States that we will send this information to.

DR. FEINBERG: Dr. Daskalakis?

DR. DASKALAKIS: First, a question for both the Partners study and the iPrEx study. Was there any baseline self-assessment of risk that was done? In other words, did people perceive themselves to be at risk?

DR. BAETEN: In Partners PrEP, we did not ask a formal standard question on self-assessment of risk, although individual and especially couples counseling, actually quite extensive couples counseling, was part of the screening process. So individuals understood their risk from being in a known serodiscordant relationship before entering the study.

DR. GRANT: In iPrEx, similarly, we had some questions regarding perceived level of risk, but they are in the computer-assisted structured interviews that have not been submitted to the FDA. But I think it is clear from our recruitment that everyone came to the study because they felt that they were at risk for HIV. That was a motivation for wanting to take a pill and evaluate whether

there was a new approach for prevention.

DR. DASKALAKIS: Just a follow-up question, specially on iPrEx. The drug levels that were correlated with unprotected receptive anal intercourse, that was based on their initial time point of report of URAI. Yes?

DR. GRANT: No. That analysis that I presented in the core presentation, that was at the time of the drug level analysis, and it reflected the previous 12 weeks.

DR. DASKALAKIS: Great. So that answered my question. And then I think my next question's going to be for the FDA, from the perspective of the REMS. I wanted just to get some information about your slide 13 -- thank you very much -- regarding stakeholder feedback.

Could you tell us a little bit about what that structure was from the forum and how that feedback has actually led to the shape of the REMS?

DR. YANCEY: Can you pull up slide 13, please? Carolyn Yancey, Food and Drug Administration, Division of Risk Management.

This slide was based on what we heard by attending the Forum for Collaborative HIV Research. It was August 2011. So as I presented this, this was our perspective on a full day's meeting and what we heard from a diverse audience, as well as panel, about what was agreed upon, people wanted, if you will, and what people wanted to avoid.

DR. DASKALAKIS: I'm sorry. In the context of that, was it a larger meeting? Was it a survey? Just what was the structure of that feedback?

DR. MURRAY: Okay. This is a workshop with a forum for HIV collaborative research here in Washington. And so we've done a lot of workshops with this group for HIV and hepatitis C-related issues. They bring public and private partners together. And so it was government and academia and insurance companies and providers, and there were several sessions.

It was a full day. And it was mainly to talk about if PrEP was implemented. And we tried to have a mitigation strategy, could a restricted distribution even be feasible in this setting of

Truvada being appropriate for -- I mean, being approved for treatment?

So I think it was pretty clear, although there was no vote or anything, but it was pretty clear from the discussions that it didn't seem feasible for there to be a restricted distribution for PrEP when it was already available for treatment.

DR. FEINBERG: Jeff, so do you mean restricted in the sense that -- like acne drugs for women, or where you have all kinds of documentation to hand to a pharmacist before you get your prescription? Is that what you mean by restricted? It's not clear to me.

DR. MURRAY: Like Accutane or other, where you would need to show a lab test showing that you didn't have neutropenia or that you have a positive test. And then the pharmacist has to check that before they will distribute the drug because some clearly HIV-positive people needed to take this drug as well.

Then, even though tenofovir is only approved

for hepatitis B, some people are using Truvada for hepatitis B as well. So it would have created a lot of problems with pharmacy delivery and prescriptions.

DR. PADIAN: Sorry. Could I just ask a question exactly about that, on the restricted access? Sorry. Nancy Padian.

So is the restricted access the justification for not requiring an HIV test?

DR. MURRAY: Well, I don't know if I understand your question. I think we are all for frequent testing and testing being done when used for PrEP, although that would have to be -- I don't think it could be mandatory, or we didn't think it could be mandatory for a pharmacist to fill the prescription.

So the pharmacist -- so the distribution of the drug would not be contingent upon a pharmacist or a clinic verifying that a test was actually done. That would have to be left up to the provider, the direct provider, and patient.

DR. FEINBERG: Let me step in here because I

think I can help clarify this, Nancy. So one way to go about it is you have to have a piece of paper you hand to a pharmacist that says, I have a negative pregnancy test. Give me my Accutane. Or another way is, I'm a registered physician. I can write a prescription for thalidomide, but other people can't.

But I don't think we're saying that from a healthcare provider point of view, they shouldn't be testing people and getting a negative test. I think the context here is, does somebody have to show proof of a negative test to some third party to get a prescription?

DR. PADIAN: I understand that. But I guess something that at least crosses my mind is potentially the use of rapid tests in the pharmacy. I mean, we do rapid tests now. I just wondered if that had been considered.

DR. MURRAY: Well, that might have been part of the discussion. But the rapid test has a window period as well. And then I guess privacy issues, and then again, a lot of people would be getting

for treatment of perhaps hepatitis B. It was discussed, but these approaches didn't seem feasible.

DR. DASKALAKIS: I'm going to grab my floor back for one second to get my last question, if that's okay. There's some discordance in the REMS presentations about a targeted prescriber, and one of the ones that I was curious to hear about was the emergency medicine physician, who may -- is that someone who is a targeted provider or not? As a point of clarification.

DR. YANCEY: Yes. Carolyn Yancey, Food and Drug. Yes, emergency medicine physicians were included in our proposed target prescriber list.

DR. DASKALAKIS: It wasn't on their list just now.

DR. YANCEY: If you turn to slide -- it's in my presentation.

DR. DASKALAKIS: It's in yours. But I think what just went up didn't show ER.

DR. FEINBERG: I believe it was on their list, too, Demetre.

DR. RAWLINGS: Madam Chairman?

DR. FEINBERG: I'm sorry. I was looking for something at the same time. Please go ahead.

DR. RAWLINGS: The question of which of the educational components that we're talking about, there are things that are asked, though, specifically within the context of the REMS. What we're describing is -- what I showed you a slide of is what we're doing in addition to the REMS.

So yes, the emergency room physicians are in the list of grouping that will get information within the context of the REMS as it's put forward. What we're describing is we're going to reach out to all of the providers that are listed in the context of the slide that I put forward.

DR. FEINBERG: Dr. Glen?

DR. GLEN: Thank you. Yes, I had two questions. First of all, congratulations to the investigators for some very nice and landmark studies.

I was wondering about the potential for asymmetric distribution of HIV exposure prevalences

between the placebo and Truvada treatment groups. And the reason that came to mind is because if we look at the patients who came into the study infected, that out of the ten, eight of them were in the placebo group and only two in the treatment.

So if there were a similar asymmetric distribution in the overall patient populations, that could mitigate somewhat the effect of risk reduction with the drug. I mean, I notice there were some -- a younger patient population, which has a higher infection rate, but that couldn't fully account for that. I was wondering if you had any thoughts about that. Then the second -- and also, that showed up also in the Partners study, and was twice as many, I guess, in the placebo than in the Truvada group.

Then the other question was the follow-up on something alluded to, and specifically if you were able to go back and look at the patients on the study who became positive. What was the longest time that someone could be RNA-positive and still not develop resistance on PrEP treatment?

DR. GRANT: Many great questions there. Slide up, please. Indeed, in the iPrEx study, the age at baseline was nine months older in the active arm compared to the placebo arm. And age was associated with less risk.

So we performed an efficacy analysis that was adjusted for age. The unadjusted efficacy analysis, including all the data through the period of treatment, showed an efficacy of 42 percent with a confidence interval of 18 to 60 percent. When adjusted for the 9-month difference in age at enrollment, the efficacy estimate was 41 percent, so very similar in that regard.

In terms of baseline risk, I showed a slide somewhat earlier indicating that the mean numbers of partners reported in the last 12 weeks in the active and placebo arm was both 18. As we move down, all of the indicators of risk at baseline, there's really comparable self-reported levels of risk.

The difference between eight acute infections in the active arm -- excuse me, in the

placebo arm -- eight in the placebo arm versus two in the active arm approached statistical significance in terms of being a difference, but the P-value is .06. We think that that kind of thing can happen by chance alone.

In terms of reported risk behavior over the course of the study, incidence of herpes, incidence of syphilis, it's really comparable in the two arms of the study. Both the active and placebo arms of iPrEx had similar indicators of risk, both self-reported as well as infectious disease biological indicators.

There were many questions there. Was that -- oh, how long could someone -- the longest that someone was RNA-positive before seroconverting in iPrEx was 12 weeks. There was only one person like that. The vast majority were -- excuse me, it was 8 weeks. That was the longest. The 17 percent who were RNA-positive before they were antibody-positive were RNA-positive just 4 weeks before seroconverting. And the window period was the same duration in the active arm and the placebo arm.

DR. BAETEN: Slide up. In Partners PrEP, baseline behavioral characteristics were comparable across the three study arms. We had five, three, and six baseline infections across the three arms. The difference was three and six between the emtricitabine/tenofovir and the placebo group, although it was five versus six for tenofovir alone versus placebo.

I showed earlier the incident STIs during follow-up, which was comparable across the three study arms, suggesting that there was comparable risk across the groups.

DR. GLEN: So just to clarify, in the materials we got, I think it was 3, 3, and 6. You say it's now 5, 3, and 6?

DR. BAETEN: The baseline infections --

DR. GLEN: Yes.

DR. BAETEN: -- are 5, 3, and 6 across the infected baseline. There were 14 infections, 5, 3, and 6.

DR. FEINBERG: Dr. Giordano?

DR. GIORDANO: Thank you. I have two

questions. The first is, there was a lot of comment from the public regarding GI side effects of Truvada. And we, I think, have focused a lot on renal effects. I don't recall seeing the data on GI side effects in both the studies. If that could be presented, please.

DR. CHENG: So I'll ask Drs. Grant and Baeten to speak to the GI side effects in the iPrEx and Partners PrEP studies.

DR. GRANT: Slide up, please. In fact, this is a comparison of adverse events related to the gastrointestinal system in the active and placebo arms. Importantly, the proportion of each cohort complaining of diarrhea was comparable, 8 percent in the placebo arm and 7 percent in the active arm. So there was no association between use of Truvada PrEP and diarrhea at all.

There was an association with abdominal pain. Typically, this was in the first few weeks of PrEP use. It was 4 percent in the active arm and 2 percent in the placebo arm. It appeared to be generalized abdominal pain, because when we

coded this as upper abdominal pain, there was no association. Also, there was no association between the arms and flatulence, gastritis, gastroenteritis.

Nausea as a grade 2-plus AE was reported in 2 percent of the active arm, 1 percent of the placebo. We also assessed nausea by medical history at every visit. And in fact, we see that nausea was reported by 9 to 10 percent of the active arm and only 5 percent of the placebo arm at week 4. But after week 4, the complaints of nausea -- slide up, please. So this is what I'm explaining now. So after week 4, the complaints of nausea in the active arm returned to placebo levels.

So we're seeing abdominal pain and nausea in early weeks of PrEP treatment, but we're not seeing diarrhea and other gastrointestinal side effects. And this is rarely a cause of stopping PrEP in iPrEx.

DR. BAETEN: In Partners PrEP, the results are similar. Slide up, please. For nausea, this

is assessed by a targeted tolerability questionnaire that was administered to the subjects every month during the study, and is regardless of grade. So this is any report of nausea in the past 30 days.

We can see it's slightly higher during month 1 in the two active arms compared to the placebo arm, but still at approximately 6 percent versus 4 percent, and then declines to comparable levels through the duration of study follow-up for nausea. Slide up, please. Similarly, for abdominal pain.

Then -- slide up, please -- for diarrhea. Slide up, please. Thank you. And similarly for diarrhea; had less than 5 percent of study subjects reporting diarrhea at month 1, slightly higher in the active arms versus the placebo arm, but then comparable thereafter for the active arms. No statistical significance after month 1.

DR. GIORDANO: Thank you. That's very helpful. I had a second question, if I may, or no?

DR. FEINBERG: Before you go ahead with

that, I think Dr. Ellenberg had a question relating -- and Dr. Blower had a question relating to what just happened here.

DR. ELLENBERG: Yes. The slide that you showed with the iPrEx data said that that was grade 2 and above. I don't know what these definitions are. I suspect with diarrhea, even grade 1 might be troublesome to people. I don't remember really remember.

I notice that the slide for Partners, you said, was all grades. But I would like, if you have it for all grades of diarrhea, for -- I'm just trying to get a sense of the difference between the no difference here and the emphasis from the people who spoke.

DR. GRANT: So in iPrEx, clinical adverse events were reportable if they had grade 2 and above. We also asked a symptom survey at every visit in history, and there was no difference in diarrhea complaints on that symptom survey.

DR. FEINBERG: Dr. Blower, did you have a follow-up question that pertained to that? And

then we'll go back to Dr. Giordano.

DR. BLOWER: I was going to ask about resistance.

DR. FEINBERG: Well, then, let's hold it and let Dr. Giordano finish because I've got you on my list.

DR. GIORDANO: Second question is regarding the REMS. The REMS uses the phrase "serostatus," assure a negative serostatus before and then during treatment. To my mind, that means standard antibody testing, yet it seems like this is a very high-risk population. There's incidence of acute HIV at baseline and during follow-up that would be better detected with not just a serostatus, but a serostatus and antigen status approach, either a fourth generation test or a viral load test.

Is that encompassed in that language in the FDA's mind when we say serostatus in the REMS?

DR. MARCUS: I'll address that question. That is one of the questions that we're asking the advisory committee today to comment on.

DR. FEINBERG: Dr. Yancey [sic], can you

just move your mike closer to where you're speaking, please?

DR. MARCUS: That is one of the questions we're posing to the committee today, as to what you would recommend in terms of testing. The serostatus does imply antibody testing, but we do want your feedback on what kind of testing would be most appropriate.

DR. FEINBERG: Dr. Van Dyke.

DR. VAN DYKE: I have two questions, a very quick one on the Partners study.

For the toxicity analysis, what was the median or mean duration of follow-up?

DR. BAETEN: Median follow-up was 23 months.

DR. VAN DYKE: Twenty-three? Thank you.

Then also -- this is a follow-up from a question that was asked about four hours ago; this is actually on the iPrEx study, and it relates to the ineligible subjects in the iPrEx study. I think the question was asked about the other reasons, and there was a slide that showed 186. But on slide 32, it shows 504 other reasons. I

also wanted to know about the 405 who were lab ineligible, what those laboratory features were.

DR. GRANT: So there could be more than one reason why people were ineligible for the study, and that would be why the numbers don't add up. People typically did have more than one reason. Slide up, please.

This is the listing of ineligible to enroll by lab testing. Two percent of those ineligible to enroll had abnormally high creatinine. Three percent had an ALT more than twofold in the upper limit of normal. We did allow enrollment of people who had AST and ALT that were less than twofold the upper limit of normal, but if it was more elevated than that, they had to be excluded, people with elevated platelet counts or thrombocytopenia; total bilirubin elevations more than two and a half-fold the upper limit of normal; absolute neutrophil less than 1,500; total hemoglobin that was less than the amount allowed. So those were the laboratory ineligibilities, mainly creatinine, AST, and some hematologic parameters.

DR. VAN DYKE: Do the others again. Because you showed a list before.

DR. GRANT: Slide up. This is the slide I showed before, other reasons for ineligibility to enroll. These others were just difficult to code. If someone wrote something into the blank, then those would be listed there as 186 out of 4,900-something.

DR. VAN DYKE: I don't understand what the 504 others are in that first slide you showed. If it shows 186 there, so who are the other couple hundred?

DR. GRANT: Oh, that's not the sum of the above column. 186 would be other reasons. So the other reasons that were specifically specified are listed above, 93 plus 56 plus 50 plus 33. And then you add up all of that plus the 186, and that will add up to more than 504 because there can be more than one reason for ineligibility to enroll.

DR. VAN DYKE: Maybe I'm tired.

DR. GRANT: Can we keep that slide up? I think that he wants to --

DR. VAN DYKE: No. The flow sheet.

DR. GRANT: Oh, the flow sheet. Slide up, please.

DR. VAN DYKE: So how does the 186 refer to the 504?

DR. GRANT: The other chart that I gave will give all of the different reasons why there would be other reasons for not enrolling other than being HIV-positive at baseline, having laboratory ineligibilities, or low HIV risk.

So that other table was the listing of all other reasons, and some of those could be enumerated specifically, but then even after that, there's some sort of non-categorized ineligibilities. And people, to be sure, can have multiple reasons for being ineligible for the trial. So it all adds up to 504 that had other reasons of some type, either specified or not.

DR. VAN DYKE: Okay.

DR. FEINBERG: Mr. Sharp.

MR. SHARP: Hopefully this will be quick.

Was HCV an exclusion?

DR. GRANT: No. HCV-coinfected participants could be enrolled in the iPrEx study. We had very few. We might be able to bring up a slide at some point. Yes, slide up.

There were nine in the active arm and five in the placebo arm who had confirmed hepatitis C infection in iPrEx. So they were eligible, but there just weren't very many.

MR. SHARP: And were any found during the study? Any additional?

DR. GRANT: No. No additional cases were found during the study. But we did not routinely check unless they had clinical or laboratory evidence of hepatitis.

MR. SHARP: Okay. And then what's the origin of the back pain? Because it seemed to be more of an issue, more of a larger quantity than some of the other side effects. Do you know?

DR. GRANT: The back pain, I believe, was reported in the CDC safety study. That might be a question for Lynn Paxton. Did you --

MR. SHARP: Did she leave?

DR. PAXTON: Although it was statistically significantly reported more often in that group, we have no particular etiology that was consistently responsible for that in that study.

DR. GRANT: We do have data from iPrEx. Slide up, please. So this is the number of participants reporting back pain over the course of the iPrEx study. There were 62 participants in the placebo arm and 59 in the active arm, not a statistically significant difference in reporting of back pain.

MR. SHARP: And I believe it resolved, too, right, after --

DR. GRANT: In iPrEx, we don't have specific data on that. Typically some back pain resolves, other doesn't. I can look into it if that's an issue.

MR. SHARP: I bring that up just because you always relate back pain to kidney pain. So I'm wondering if there's some kind of correlation there.

Then one more quick question regarding the

REMS. So why was the decision made to not have a registry? I may have missed that.

DR. CHENG: I should clarify. Dr. Peschel will come and clarify that we will have a registry, and he'll explain the details of that registry.

DR. PESCHEL: So the question was, why was the decision made not to have a registry? Did I understand correctly? I think we have to distinguish two different types of registries. There's, for one, the registry that could be part of a REMS like a control distribution. So in other words, every patient, every prescriber, has to be enrolled in the registry, and without that, they could not prescribe or get drug.

That would be a restriction similar to what was alluded before. And that registry was not considered. We are, however, proposing from Gilead's perspective a voluntary prescriber and patient registry. Slide up, please.

As you can see here, what we're intending to do -- in fact, with all our supporting measures, we are attempting to support the key risk messages of

the REMS. So one of the messages is, testing is critical. We are providing free HIV and HBV testing. Truvada is only to be used as part of a comprehensive prevention strategy. Part of that, and the most efficacious part, are condoms, so we are providing free condoms.

There are a variety of unresolved questions, so we will support demonstration projects who will hopefully get us answers around behavior, adherence, seroconversion. But those will probably focus mostly on specific groups and regions. So we intend to supplement that with a broader approach that depicts real-life scenario as far as possible, and that is the proposed registry.

What we intend to do is involve prescribers and patients, and follow them longitudinally over the course of 3 years via, again, knowledge, attitude, and behavior surveys that will be very similar to the ones used in the REMS, except the REMS will use a snapshot in time, whereas the registry will follow the cohort longitudinally over time. And the results from all of that will be

included in our annual REMS assessment reports to FDA.

So, as you can see here, we're planning initially to enroll about 250 prescribers and a thousand patients. But we are open to expand that, if there's enough interest. And then we will survey prescribers every year and patients every half-year, repeatedly.

We also encourage patients who are -- whether they are on PrEP or off PrEP, should they use PrEP intermittently, to stay in the registry. And the intent is really to get some answers around adherence. Does risk behavior change? Is there intermittent use? How is the drug used in the real world scenario in support of these demonstration projects that will already have 32,000 patients enrolled.

MR. SHARP: And safety as well? Any kind of safety being tracked in this registry?

DR. PESCHEL: We actually have a variety of safety measures, just not as part of the registry. The registry is really based on surveys to keep it

as open as possible.

What we intend to do from a pharmacovigilance perspective -- and I think we have a slide -- we, as any pharmaceutical company, are obligated to have ongoing pharmacovigilance. And we have been following Truvada since 2008 -- 2004, excuse me -- and its component, tenofovir, basically since 1998. And that's where we have accumulated the 9 million patient-years of exposure, and that's what Dr. Cheng alluded to before. Slide up, please.

In the course of this ongoing pharmacovigilance, what we do there is we collect data both from clinical trials as well as from postmarketing from worldwide sources, including the literature that we scan regularly.

We put those data in the global safety database. According to the regulations, there are a variety of time frames that depend on the seriousness of the case, but some cases have to be reported to agencies worldwide in 15 calendar days.

But all of those data get evaluated in

regular time frames through so-called periodic safety update reports. Truvada is currently on an annual schedule, so on an annual basis, we evaluate retrospectively the safety profile.

Now, for PrEP, we want to add a few measures that are also targeted at adherence, but also, for example, resistance and seroconversion. So from a data collection perspective, we will introduce specific structured follow-up questionnaires for all reports of lack of effect to ask about adherence, risk behavior, potential resistance, and so forth. That data will be added to our global safety database.

In addition to that, with all the projects we support, and that includes all the demonstration projects, we put safety data exchange agreements in place that obligate the party that we support to report all adverse events to us. All of that data gets into our global safety database, and in those aggregate reports that we issue annually and that go to agencies worldwide.

We will also have a specific section about

PrEP, where we will look specifically at potential new signals that have occurred in PrEP by comparing it to what we know about the safety profile in treatment of Truvada.

The structured follow-up plus -- it was before mentioned, one of our supports for the regular testing is subsidized, the free testing, in case of seroconversion. And in order to get the free testing for seroconversion, the prescriber would have to call our medical information department. That means that they will talk to a medical information specialist who is trained to take this in as an adverse event, and it would come again to us into the global safety database. So we would get data around all of this from a variety of sources, and it's all linked together and then gets evaluated regularly.

MR. SHARP: Thanks. That clarifies a lot.

DR. FEINBERG: It's 5 after 5:00, and we're going to allot 10 more minutes to clarifying questions because we have still a great deal of work to go. And I'm going to take the chair's

prerogative, at least, to ask my question, and then we'll see if we can get these things done quickly.

So Dr. Cheng, you presented data for us on the renal safety of Truvada as assessed in treatment studies. And we've heard about the renal outcomes from the two studies, and they all look reasonably bland.

I think we heard, as these things were being presented, that people with preexisting renal insufficiency or diseases that would augur for problems with the kidney were largely excluded from most of these studies. Right? You couldn't get into 903 or 934 if you had, whatever, uncontrolled hypertension, diabetes -- I'm asking because I wasn't an investigator so I don't know the question. But --

DR. CHENG: Sure. I'm happy to respond to that. For the registrational studies, 903 and 934, there are no exclusion criteria for diabetes or hypertension.

DR. FEINBERG: So there were just criteria for renal function within a certain range?

DR. CHENG: Correct. For study 903 --

DR. FEINBERG: Okay.

DR. CHENG: I'm sorry.

DR. FEINBERG: So I'm struck by the fact that in clinical practice, I think many of us see a great deal more nephrotoxicity than has ever been presented or published from these studies. And I think I remember that the definitions of grade 1 toxicity are relatively liberal.

I think you showed us on slide -- here we go -- on slides 12 and 13, where you had changes in creatinine and graded changes in proteinuria, so they could have gone up to 6 and a half percent grade 1 in creatinine, and up to 27 percent grade 1 proteinuria.

I think it would be helpful if you told us, what does grade 1 mean in these two instances? So we can really understand -- grade 1 sounds very bland, but what does it mean?

DR. CHENG: That's a difficult question to answer. It should be easy, but -- we were asked to collate past registrational studies, some of whom

are ours, but many of these studies in this study are not ours. And they're published literature, whether they be for, let's say, rilpivirine and Truvada or other studies.

As such, the grade 1 criteria for these differ from trial to trial. And even in our own trials -- let's say study 903 -- we used a grade 1 serum creatinine of a 0.5 milligram per deciliter increase over baseline; whereas in study 934, we used 1 and a half milligrams per deciliter, regardless of where the baseline was.

So that's why, when I mention these studies, it's a little bit difficult to amalgamate them from trial to trial because most of these are not our trials, and we're not aware of what the grading criteria is for these. These are from the published literature. It's not always clear what grade 1 is.

DR. FEINBERG: So if I understand what you just said correctly, so grade 1 for the company-run studies was half a milligram above baseline. That's what would have been considered a grade 1

increase?

DR. CHENG: For study 903 only. For study 934, which was conducted three years after we conducted study 903, we ourselves changed the grading criteria to grade 1 would be 1 and a half milligrams per deciliter, absolute. So anyone, regardless of where they started from, it's not a change over baseline.

DR. FEINBERG: Okay. And then in the iPrEx and Partners PrEP, you used the Division of AIDS grading scale? Tell us what grade 1 means in your system. Because, of course, as you're walking to the podium, half a milligram increase for somebody who already has creatinine of 1.2 puts them in a different category than a person whose baseline creatinine is .6.

DR. BAETEN: Absolutely. Slide up, please. In Partners PrEP, we used the Division of AIDS grading scale and we modified it with some conservative parameters for grade 1 and grade 2. So the Division of AIDS grading scale for grade 1 toxicity, creatinine toxicity, is 1.1 to 1.3 times

the upper limit of normal.

Next to that in smaller print is what that would translate to for Partners PrEP, would be 1.4, or 1.23 for women. But we also said that any result that was 1.5 times baseline, regardless of what baseline was, was also a grade 1 creatinine.

For grade 2, the Division of AIDS is 1.4 to 1.8 times upper limit of normal. We said, in addition to that, any creatinine clearance that was less than 50. Nearly all of our -- if I could have the next slide up, please -- we had six confirmed grade 2 creatinines during the study.

Four of the six were grade 2 based only on that creatinine clearance of less than 50, and they all resolved with discontinuation of product. And then -- next slide up, please -- in addition, there were 46 grade 1 events that were confirmed in the study. Nearly all of those in the top row are only 1 and a half times baseline. They are not in the Division of AIDS grade 1 otherwise. So they are at our most conservative criterion for defining grade 1.

DR. FEINBERG: How was that different, Bob, in iPrEx, or the same?

DR. GRANT: So in iPrEx -- slide up -- in iPrEx, it's really the same grading system as in Partners PrEP. We used the DAIDS grading table, but in addition, we do have this criteria of grading as a grade 1 creatinine elevation if there's a 50 percent increase from baseline, even if that continues to be in the normal range.

But there is a difference between Partners PrEP and iPrEx in that we reported as adverse events any creatinine elevation, even if it was not confirmed on a separate specimen. And I believe in Partners PrEP they reported it as an adverse event only if it was confirmed.

Typically, in the context of clinical trials, you're seeing rates of confirmed creatinine elevations. In iPrEx, the vast majority of creatinine elevations resolve within 7 days when we collect a separate specimen. They appear to be due to transient issues such as dehydration, exercise, a variety of other things that can transiently

increase creatinine this very small amount like what we're seeing here.

DR. FEINBERG: Although nonadherence means that people didn't get a full exposure, and people in these studies were a median of 23 months. These were not the kinds of toxicity issues we see when people have been on these drugs for years.

So I guess the answer is although the criteria are somewhat different, the definition of grade 1 is rather generous. I don't think any of us would be happy with a 1.3 times upper limit of normal creatinine if we went to our doctor. That was a judgment comment. But --

DR. GRANT: Did you mean 1.3 times the baseline? Because 1.3 times the upper limit of normal would clearly be within grade 1 for DAIDS criteria, regardless of which study.

DR. FEINBERG: Yes. But what I'm saying is, I think those criteria are very generous for -- since it's a logarithmic dropoff in renal function, those are rather generous criteria by which to define a grade 1, which you generally think of as

being a modest change.

Okay. I had my question. I've got one, two, three, four, five, six, seven other people. Let me call briefly on people who haven't spoken.

Dr. Wood?

DR. WOOD: Thank you. Lauren Wood, NCI. We've heard from both investigators and the sponsors how critically important adherence is. And in your proposal for the indication, as part of your education program, you specifically state that, "All uninfected individuals should be counseled to strictly adhere to their Truvada."

I would like to know from the sponsor's perspective how you would define strict adherence, how you would propose defining strict adherence. That's my first question.

DR. CHENG: I'll ask Dr. Rawlings to come speak to that.

DR. RAWLINGS: Based on the data, we are defining that as being daily use.

DR. WOOD: So greater than 90 percent?

DR. RAWLINGS: Yes.

DR. WOOD: Okay. The next issue has got to do with the issue of adherence. I think there's been an automatic assumption that if tenofovir was not detectable, it reflected individuals not taking their medication.

However, it is possible that increased clearance of the drug could result in nondetectable levels of the drug. There are a couple of published papers about population pharmacokinetics of tenofovir in individuals with AIDS, but increased clearance was related to body weight to serum creatinine ratio -- higher body weight to creatinine ratio increased clearance of tenofovir.

So I'm curious. As the sponsor, do you have any data at all that looks at either weight or BMI, and the detection or the ability to detect tenofovir?

My concern is twofold. One, we have a huge obesity problem in the United States of America. In the populations that are disproportionately affected with HIV, lower socioeconomic status, oftentimes females, obesity is an issue. You also

have presented data that suggests that individuals who had lower weight had increased incidence of toxicities observed, which would suggest lower weight, decreased clearance.

So that's my question in terms of do you have any data about weight to serum creatinine ratios, and how weight impacts clearance, and how that may result in lack of detection of tenofovir?

DR. CHENG: I'll ask Dr. Grant to come speak to that from the iPrEx study.

DR. GRANT: Quite right. There's multiple determinants of drug level. Clearance and accumulation can differ between people. But the effect of body mass index and variation in renal function within the normal range, like we have in these studies, are relatively small effects in the dynamic range of these studies. Slide up, please.

To try to understand what it meant to have an undetectable drug level in iPrEx, we again collaborated with Albert Liu at the San Francisco Department of Public Health, who had done a study of directly observed therapy of two tablets per

week, four tablets per week, and seven tablets per week in a crossover design.

Importantly, people taking two tablets per week, 100 percent of them had detectable drug in viably cryopreserved peripheral blood mononuclear cells, not only detectable, but detectable well above the lower limit of quantitation of the assay.

So we infer from this that people in iPrEx who had undetectable viral load in their PBMCs were taking less than two pills per week, probably substantially less than two pills per week. We can't be very precise, but it was substantially less than two pills per week.

I wanted to bring up the table of number of pills per week by estimated efficacy in iPrEx to address this concern of what level of adherence do we have to have in order for this PrEP intervention to work. Slide up, please.

So this is an extension of the collaboration cited earlier, a work presented by Peter Anderson at the CROI meeting last year, in which he looked at the drug concentrations achieved by two doses

per week, four doses per week, and seven doses per week. And then he asked what level of protection could be observed with the level of drug that would be obtained with those three levels of adherence, if you will.

These are the results of that analysis, which did bring in information from the placebo arm of the trial through a method of multiple imputation performed by David Glidden.

Concentrations achieved with two doses per week were associated with a 76 percent reduction in HIV risk in iPrEx. Concentrations associated with four doses per week were associated with a 96 percent reduction in HIV risk in iPrEx. And concentrations associated with seven doses per week were associated with a 99 percent reduction in HIV risk in iPrEx.

So what do we recommend in the face of this? What we're seeing here is that we see substantial protection even with relatively low drug exposures in men who have sex with men. We still feel that a recommendation of daily dosing is warranted, for

several reasons.

One is that a recommendation of daily dosing is the only recommendation that's been evaluated on an intention-to-treat basis in clinical trials. Two, daily dosing allows for routinization of dosing. People don't have to estimate the risk of any given sexual act or any given sexual partner.

But from a pharmacological point of view, I think these data tell us that seven doses a week give us a drug level which provides some forgiveness if doses are missed. We heard a number of concerns raised by the audience, that people are people. They're not going to be able to take a pill every single day without fail.

But that's not what we're asking for here. I think that what we mean by adherence and our goal for adherence is for people to stick with the program, to try to take pills every week, and try to take seven pills per week. If they miss a few, there will be enough drug level left to provide some level of protection. That's what this analysis tells us. This is a robust intervention,

allowing for some forgiveness for human nature, if you will.

DR. WOOD: I had one more question. Were you going to respond to that?

DR. BAETEN: I can add a little bit onto this one. Slide up, please.

In Partners PrEP -- and this goes back to, actually, Dr. Morrato's earlier question about what levels were like -- in Partners PrEP, we see that 70 percent of individuals on the bottom row that should be greater than or equal to 40 have levels suggestive of steady-state dosing when we measure at any time during follow-up.

So those middle two rows between .3 and 40 may be individual pharmacokinetics, may be imperfect daily dosing, or may be factors such as BMI or other factors that would have someone have a slightly lower level, even if they were taking it regularly. This is something we're going to pursue in bringing together our MEMS data, our electronic monitoring data with our drug levels at some point. It's a very good question.

DR. WOOD: The third question had to just do with the issue of resistance, which was documented to be low. But one of the things that was present in both studies was that monitoring for HIV occurred every month.

I wonder if Dr. Mellors or someone else could speak to the issue of, if monitoring was not done every month, would the likelihood of resistance increase if individuals are on PrEP, because they would become infected and continue to receive therapy, being unaware of their HIV status? And if there's any way that modeling might be able to address that question. Thank you.

DR. MELLORS: Thank you. John Mellors. Thank you for that question.

Yes. Your instincts are right. The longer you are viremic and receive drug, the higher the theoretical risk of resistance. We don't have exactly parallel data from the treatment world, but that would be the idea.

Given that idea and given that assumption, you can model the frequency of resistance,

testing -- excuse me, the frequency of HIV testing as yearly, twice a year, every four months, or quarterly. And the model output -- and Dr. Ume Abbas at Cleveland Clinic has done this -- the model output can be the prevalence of drug resistance in the population.

You can show a sizeable difference between a year and six months, meaning a lower prevalence of resistance, if you test for HIV every six months; a small decrease going from every six months to four months; and really minimal change with more frequent testing.

But again, the caveat is, that is a model and that needs to be confirmed by other modelers.

DR. WOOD: Thank you. That's very informative.

DR. FEINBERG: Okay. Last two questions from people who hadn't had an opportunity before, Mr. Raymond and then Dr. Ruiz.

DR. BLOWER: Can I just follow up on that, the modeling question? Because I think what John Mellors is talking about actually is -- the results

in that study were actually that you could get very high levels of resistance without testing.

DR. FEINBERG: You know what? I'm sorry. If we don't stop somewhere, we're just not going to -- then we'll really be here till midnight. So hopefully it'll come up in some other part of the discussion.

MR. RAYMOND: My questions have already been sufficiently addressed.

DR. FEINBERG: Oh, okay. Dr. Ruiz?

DR. RUIZ: Thank you. And thank you, Madam Chair, for being patient with me raising my hand because I was worried that you didn't see me.

My questions are for the FDA and for the sponsor. I have some serious concerns about the REMS strategies being proposed, and the first goes to the issue of no documentation of safe use conditions.

It is strange to me why you would not want to make sure that the person receiving Truvada for a PrEP indication is not HIV-negative, especially when we know from Dr. Mellors' fine slide and from

the trials that resistance is more likely if PrEP is given during unrecognized acute infection.

It seems that having that test would not only ensure safe conditions for usage, but would also provide an opportunity to diagnose previously undiagnosed HIV infections and get people into treatment, so we're meeting that goal in terms of getting people into treatment, and lowering their vial load, and hopefully increasing their lifespan. It would help us to recognize acute infection, et cetera, et cetera.

So if I could get some explanation of why that is there are part of the REMS because it really makes no sense to me. And I have a couple other questions after that, but let's answer that one first.

DR. MARCUS: I'll try and summarize all of our discussions because we had just extensive discussions around this, both within FDA and within the forum meeting where we discussed this with stakeholders.

The issues are threefold, if I have it

right. One is having a restricted system for one indication without restricting distribution for the other indication. So we would not want to restrict access for HIV-infected patients who need treatment. They need to have full access to medication and not have any barrier created that would decrease their compliance with and success for treatment. I don't think we came up with any system that could not be circumvented where you restrict for one indication and not for the other.

The second issue really involves the healthcare system. And while we can be very creative in ideas, coming up with systems that would require restricted distribution, they often don't take into account the realities of the actual healthcare delivery system, such as pharmacies that have, for example, electronic prescription processes and handwritten prescription processes. In addition to that, they'll have payer processes, where insurance plans need to approve medications.

Having this type of system, again, with a restriction for distribution is going to create a

complexity in prescription fills that I'm not sure can be managed feasibly by a pharmacy system. And then ultimately, we also discussed the privacy issues involved around requiring the results of an HIV test be reviewed by a pharmacy in order to get a prescription fill.

So those are two of the issues. The third is one that was discussed at length in the forum meeting, is that while we were really talking about not wanting to restrict distribution to HIV-infected patients and decrease the likelihood of their successful HIV treatment, many individuals at the forum meeting told us very loudly and clearly that receiving Truvada for HIV prevention should also not be restricted, so that the patients who are perhaps most vulnerable -- the individuals who are most vulnerable and most in need of PrEP as a prevention tool should not be subject to barriers that would decrease the likelihood that they receive and comply with treatment.

DR. RUIZ: Yes. I understand those. But I think part of it still doesn't make sense to me

because everyone has a right to know their HIV status, and there are many ways where knowing one's HIV status does not have to be a barrier; for example, rabbit testing, voluntary opt-out testing as part of routine medical care. Those guidelines, I believe, have been implemented, et cetera.

But just as someone who is HIV-positive who is receiving Truvada for treatment typically, as far as I know, has to go to a provider to get a prescription for the drug that they then take to the pharmacy to get that prescription filled, the same thing would happen for someone who is HIV-negative who would want to get PrEP, would have to go to the provider, whatever that provider might be, make sure that it is safe for them to take PrEP, hence, enhancing the safety profile or optimizing the safety conditions, receiving whatever counseling they might receive as part of the total package that we're talking here about PrEP being part of a comprehensive packaging, and then go to the pharmacy to get their PrEP.

So I'm not seeing how that would restrict

access to the HIV-positive people getting PrEP for treatment or the HIV-negative people who want to get PrEP for prevention. I'm not seeing how that is that much of a barrier.

It seems to me, given so many concerns about toxicity, about side effects, et cetera, making sure that the person is looped into a system of care where they can get care if they have those side effects, where they can have their health monitored while they're taking pre, to me it seems like it would be an optimal condition.

That way, they can make sure that if they are having side effects, they can then have those side effects taken care of, maybe get off PrEP if it's too much for them. PrEP might not be for everyone.

So I think that's part of what -- I'm not understanding why this is such a barrier when, for many other health conditions, going to get a test isn't.

DR. BIRNKRANT: I think we're in agreement with what you're saying. So in other words, before

a prescription is dispensed, obviously a patient has to be tested. And then they would be instructed not to start the medication until they're notified that they have a negative test.

Now, when we get to the point of discussion of the questions, question number 2 talks about testing. So we're hoping that you'll discuss at that point types of testing, frequency of testing, do you agree with what's in guidelines, how often should patients be seen, counseled, et cetera.

We're not saying that this drug should just be given to a patient without any testing at all. Of course we want patients tested. They should be negative. And we'll elaborate, or you'll elaborate more, during discussion of question 2, how many negative tests would you need before you felt comfortable starting Truvada for PrEP?

So we feel as though that we are definitely in agreement with the comments that you've made. The examples that were brought up, thalidomide and Accutane, they require negative tests and notification of a pharmacist. And then it's at the

pharmacy level where a prescription is obviously dispensed. But if it's a positive test, you don't get the drug. Right?

So we can't really tie the dispensing of the drug to a test where the pharmacy decides, okay, I can dispense or I can't dispense. That has to be settled at the physician's office, so a discussion between the patient and the healthcare provider.

DR. RUIZ: Right.

DR. BIRNKRANT: So in other words, a review of the test results. Even with a negative test, it doesn't necessarily mean that you're negative. You have to monitor for acute infection, et cetera, for symptoms.

DR. RUIZ: Yes. Okay. I guess the point of clarification, then, came with regard to what's proposed as the REMS and whether or not we're voting on these, or whether we can change it.

So what I'm hearing from you is, we have the opportunity to change the proposed REMS.

DR. BIRNKRANT: Have input. Exactly.

DR. RUIZ: Fabulous.

DR. BIRNKRANT: Input. We're looking for input. That's why we're having this committee meeting today. We want input from you.

DR. RUIZ: Good. Excellent. That wasn't clear.

DR. BIRNKRANT: So that this drug can be used safely if you decide that it should be approved for this indication.

DR. RUIZ: Okay. The second question, I guess, is how are the proposed REMS or these perhaps maybe revised proposed REMS from the FDA meshing in with the proposed REMS from the sponsor? Because in some ways it seems like there's a lot going on over here; there's not as much going on over here. How are they going to mesh together so that the maximum data can be obtained for efficacy, safety, et cetera?

DR. BIRNKRANT: Well, clearly there has to be agreement between the agency and Gilead Sciences on what the final REMS would look like before it's initiated. So again, we're looking for advice from you on this program to ensure that this is as safe

as possible before any regulatory action is taken.

DR. FEINBERG: Well, that's a great segue. So Dr. Birnkrant, let's proceed with the charge to the committee.

Charge to the Committee

DR. BIRNKRANT: Well, thank you for this lively discussion and for your time. It was important that we had a public meeting on this topic for the PrEP indication. I think we all agree that it's very complicated.

We've heard both from the applicant and the FDA's presentations, and we've heard from the public. While this topic has the potential to be an emotional issue, the goal of this meeting is to look at the science and provide the best possible evidence-based recommendations.

You've had an opportunity to hear the safety and efficacy data from the trials that were presented today in different populations, and we are looking to you for an active discussion regarding the risk/benefit of Truvada for PrEP based on this data. I will remind you that the

application is still under review, and again, we're seeking your expert advice.

So we will be asking the committee a number of questions related to risk/benefit in different populations, which is question 1, the voting question. We'll ask questions related to monitoring for HIV seroconversion or other means for determining patients are HIV positive; toxicity monitoring; we'll ask you about risk mitigation strategies; and postmarketing studies, if deemed appropriate based on your vote to question 1.

We had a bonus question regarding future clinical trial designs, whether they could be placebo-controlled based on the results of these studies and your vote today. But, given the time issue, we can skip that one if you would like.

So I think we're ready for the first question if you are, Dr. Feinberg.

Questions to the Committee and Discussion

DR. PADIAN: Can I ask a question about the questions?

DR. BIRNKRANT: A question about the

questions? Okay.

DR. PADIAN: Sorry. What I'm confused about is -- I share some of Monica's concerns. My confusion is this, that it seems to me that the vote, to a certain extent, hinges on what the REM looks like. So if people feel strongly about wanting to change the REM in order to be able to vote one way or the other, it just seems slightly backwards. And I just was wondering about that.

DR. MURRAY: Well, I don't think that we can guarantee that your input on the REMS will necessarily be the way the final REMS could be.

Do you have comments?

DR. MARCUS: Perhaps it will be helpful for the discussion around the REMS to put up the specific elements of an ETASU. I'm not sure what you have in mind when -- I hear your concerns about requiring documentation of HIV-negative testing.

I'd like to put up a slide with the elements of the ETASUs, if I can get a slide number, so that we can understand, if you have something in particular in mind.

My thoughts around requiring documentation of HIV-negative testing means that you would have to have some kind of physician certification, and possibly other elements of an ETASU. So I want to get those up on the screen to provide clarity around this discussion, if we can.

DR. YANCEY: Carolyn Yancey, FDA. Can you put up slide number 6, please?

DR. WAPLES: Just for clarification, are we moving to question 3 before answering question 1?

DR. BIRNKRANT: No, not yet. We're just having further discussion.

DR. WAPLES: Thank you.

DR. YANCEY: Again, these are the elements that can be used in a REMS. There are six possibilities. The first is one that the agency and the applicant concur in terms of a proposed REMS, and that's education and training of prescribers.

As I understand your questions, element (d), "Drug will be dispensed to patients" -- in this case, uninfected individuals -- "with evidence of

safe use conditions." Under this clinical development program, that would be a negative HIV test.

That ETASU was considered, and considered as being linked to prescriber verification of the individual's negative HIV test result, not at the pharmacy level. Clearly, in clinical practice, our expectation is not that the pharmacist would view that information or certainly make clinical determinations off of it.

So if the proposed REMS were to include two elements to assure safe use, training and education the first one, and the fourth one, documentation of safe use evidenced in this clinical program, a negative HIV test, that would be linked to the prescriber. It would be linked at the physician level because the physician would need to see that result and verify whether or not that person could receive a prescription.

That would be considered by us as a restricted distribution. In other words, the individual comes to the prescriber. They've had

the test. The test is negative. They can receive a prescription. If that test were positive, they would not receive a prescription.

This was debated, as Dr. Marcus had shared, extensively internally, as well as very robustly discussed at the forum for HIV, for collaborative HIV research. And what the agency heard was that stakeholders did not want a restricted distribution plan linked to documentation of safe use, a negative HIV test, for access to Truvada for a PrEP indication.

DR. BIRNKRANT: Okay. Why don't you explain to us what your concerns are and how you would change what we presented to you. What we're trying to say, and obviously we're not being clear, is that we expect physicians to hold off prescribing until they have a negative test. I mean, that's standard of care. Okay?

What we're saying we can't do, because Truvada is already on the market for another indication, as are emtricitabine and tenofovir separately -- so clearly, if we had a very

restricted means of distributing this for PrEP, it could clearly be circumvented. And that wouldn't serve anyone at that point because we would be impacting negatively those who need it for treatment, and we would also be inhibiting or impacting those negatively who need it for PEP as well as for PrEP.

DR. FEINBERG: Dr. Birnkrant, I don't think that people around the table here are concerned about the restriction, for example, at the pharmacist end. As I hear the rumbles, I think what the people at the table are saying is that the elements to assure safe use, the ETASU, can't be limited to A, but in fact has to include D, that people have a negative test from their doctor or their health department or somewhere, and then they get that prescription when that known test is negative.

That really doesn't put any structural problems in front of it because we all are terribly concerned about the problem of giving this drug as inadequate therapy to someone who's already HIV-

infected; and in particular, if they're acutely infected and they have viral loads in the millions, that we're going to create a whole new piece of resistance. After all, we're talking about targeting the highest-risk people.

So I think that's the read. And I don't see how that constitutes an obstructive element. A physician has to see a patient to write a prescription -- not just a physician -- a healthcare provider --

DR. BIRNKRANT: Absolutely.

DR. FEINBERG: -- has to see the patient to write a prescription.

DR. BIRNKRANT: That's right.

DR. FEINBERG: So they draw a blood test.

DR. BIRNKRANT: Right.

DR. FEINBERG: And we can argue about antigen, antibody, and viral load. And then they release that prescription when that test is negative.

DR. BIRNKRANT: Right. Right. And in my mind, that's standard of care for a practicing

physician in 2012.

DR. STRADER: So what you're saying is that they do not then have to present the evidence of their negative HIV test to the pharmacist to get the drug?

DR. BIRNKRANT: Correct. Right.

DR. FEINBERG: And I don't think we think about that. But I guess my concern is the assumption that this is standard of care when you're talking about the potential prescribers are family doctors, internists, pediatricians, people in all kinds of healthcare settings that have no familiarity specifically with the management of HIV.

So I think the assumption that that's standard of care is dangerous when we're talking about letting 200,000 healthcare providers know about this. I think that the REMS has to indicate that the healthcare provider must have a negative test in hand, and then we'll argue about what that test is, before that prescription is written.

DR. MARCUS: Can I just provide one

clarification? For a program such as Accutane, where you are required to have a negative pregnancy test, the gatekeeper, so to speak, is the pharmacy. I'm not sure how one would enforce requiring a physician to have a negative HIV test. Who is going to monitor that that has been done?

There is no system currently in place where if some kind of condition of safe use is required, such as a negative pregnancy test or normal transaminases, the gatekeeper is the pharmacy. We don't have a system where it stops at the physician. I'm not sure how that would be enforced.

DR. FEINBERG: Dr. Morrato?

DR. MORRATO: Yes. We had the isotretinoin program reviewed by the DSRM committee in December, and so I wanted to check my memory, and also having been a mother of a patient who was on the drug. The doctor reviewed our lab results, and it wasn't until the doctor released the prescription to the pharmacy and then the pharmacy verified that, that we got the prescription.

So the decision-making was the doctor looking at the lab results. And then the pharmacy is the one that is the last resort, and they're checking to make sure that link occurred. But it wasn't like I had to take lab results to the pharmacist.

DR. FEINBERG: I would also say that this is an imperfect concept in an imperfect world, that I understand that there's no way the FDA can monitor each healthcare provider to make sure he or she has done the test. But if it says that this is what you're supposed to do and that healthcare provider doesn't do it, well, there's a lot of lawyers that would be happy to hear from that patient. So I think fear of litigation might keep people more in line. No one's expecting the FDA -- I will speak for myself.

DR. BIRNKRANT: But let me just ask another question, then. How would you handle, then, those patients who are infected? Who are on treatment, I meant? So how would they be handled in order for them to get their prescription?

DR. WOOD: One of the things that you could do is the Truvada preparation for PrEP could be named something different. It's the exact same formulation, but it has a different name. And because it has a different name specifically for the PrEP indication, that way there's no confusion.

People who are receiving Truvada for their antiretroviral treatment come to the pharmacy and they get the Truvada. If they then are getting Truvada-X, there has to be that follow-up with the physician. And that allows the separate tracking specifically, actually, at a pharmacy level of the number of patients who are actually pursuing using Truvada for a PrEP indication.

DR. FEINBERG: Doesn't that exist for bupropion? Aren't there two names, one for the antidepressant and one for the quit smoking?

DR. BIRNKRANT: I think it's a different dose.

DR. MARCUS: That drug's not restricted, so there's no issue with prescribing one versus the other. Now, if you have two drugs with

different -- Truvada for PrEP, Truvada, the system can be circumvented just by writing a prescription for one or the other.

Also, getting back to the -- and I think we might get hung up on this issue of requiring an HIV-negative test as a requirement for getting a prescription. The pharmacy is supposed to verify that the physician has conducted the necessary test before writing the prescription.

Now, if that is not a requirement that the pharmacy verify that, then some mechanism is going to have to be in place for an assessment of the risk evaluation and mitigation strategy for documentation of an HIV-negative test. So that would mean that prescribers would have to be identified so that their records could be reviewed. That would be part of an assessment. That I think would necessitate the discussion of having a healthcare provider registry for prescribing Truvada.

Then we run into the issue of having a single drug with a single packaging for Truvada

that you'd have to be able to identify that a prescription has been written appropriately for the appropriate patient.

So my only point is that this may sound simple in principle. But I think the actual implementation of a REMS with an ETASU to require documentation of HIV testing is more complex than would initially appear because assessment of the ability of this REMS to mitigate the actual risk is part of the REMS.

DR. FEINBERG: I guess what I would say about that is -- what I was quite struck by when I read the proposal for the REMS -- is it's extremely passive. Okay? You send a pamphlet to 200,000 doctors. They read it. If they want to go online and take a self-assessment test, they can. But if they don't want to bother, they don't have to.

So I have a hard time understanding, in a system that's utterly passive, how you're going to know that your risk mitigation is working as well. So I don't see that as being any better or worse than saying, prescribe this after you have a

negative HIV test.

I think the potential harm here is stupendous. And I think if we were to -- my personal opinion is that if we were to obviate that, if we were not to pay attention to that, we would have the potential here as an advisory committee to do more harm than good, and that concerns me greatly.

MR. RAYMOND: I want to speak as somebody who was actually at the Forum for Collaborative Research meeting where these issues were discussed because I don't think that's a perspective that's been widely shared here.

I think the concern for -- I would make a distinction between the various tools that we have to ensure that, for example, people do get tested and screened for acute infection before they're diagnosed [sic] with PrEP. There are some multiple tools. There's labeling. There's medical education. There are clinical guidelines. There are e-reminders and electronic -- we have multiple tools, up to and including a REMS.

But the REMS is really, from my perspective, from a -- I don't want to claim this as the universal community perspective. But I think REMS is really to safeguard against serious and imminent harms that require a certain amount of check and balance, and where there's a system that can also be assessed and evaluated to see if it's working as intended.

To me, having a negative HIV test prior to being prescribed medication is not that different than most routine prescriptions for blood pressure or hypertension or stuff like that. I think my concern is that with an ETASU, inevitably what's required to put in place this restricted access will in fact restrict access.

I mean, we see that more and more with prescription painkillers. Rightly or wrongly, it's about striking this balance between risk and need. Right? And if we put too many hoops to jump through, then there will be people who will not make it through those hoops.

The question, I think, that we're talking

about is, are the people who will not make it through those hoops are those people who actually have acute HIV infection and would be harmed because it wouldn't be caught, or are those people in need of better prevention tools who would be left vulnerable to infection?

I think, thinking back to the forum meeting last October and thinking back to the complexities of how do you meld a system where there's already an indication for treatment for people who are HIV-positive as well as those people with chronic hepatitis B who are monoinfected who are using it, I am just concerned that there's no way to ensure that safeguard.

So we have to fall back on the traditional things like labeling, like medical education, like clinical practice guidelines, that we have always used to make sure that people get good and proper care. Thanks.

DR. FEINBERG: Dr. Birnkrant?

DR. BIRNKRANT: The labeling for Truvada already has a boxed warning for lactic acidosis and

use in the setting of hepatitis B. So we could clearly add wording to address the issue that you must have a negative test before receiving Truvada for a PrEP indication.

In addition, we can work with partners at the CDC level. I'm sure at some point that they'll have some recommendations with regard to using PrEP in addition to their interim guidance. And perhaps there are other ideas that we could investigate as well to be able to help to ensure that this will be used safely when it's used for PrEP, in combination with other prevention strategies.

DR. FEINBERG: Dr. Robinson?

DR. ROBINSON: Yes. Unless I'm reading the discussion around the table wrong, I think we're working very hard at -- we're agreeing with each other in that, first, we don't want an untenable barrier to the patients who need the access and need it easily. Secondly, we want some assurance that the mistake will not be made to give the prescription to somebody who's got an unevaluated acute infection.

I think the resolution is, as Dr. Birnkrant has suggested, in the label, included in the guidelines. And there is a mechanism that is already proposed in the REMS that could be used to monitor that through the behavioral surveys. So I think with that package, plus some level of confidence that physicians are not going to be too stupid about this, should be sufficient, I would think.

DR. FEINBERG: I guess I agree with you that we have those basic understandings. But if we are going to put it in the label, why would it not be in the REMS? That is the part --

DR. GIORDANO: The REMS is saying, it's got to be there, and it's got to be documented, and in order to continue to dispense, it's got to be proven every, single month. That's how I read the REMS. Maybe I'm reading it wrong, but I see this as a discussion around what's absolutely required by statute, practically.

No one is going to give the medicine unless it's documented, versus what we can strongly

recommend and what we can clearly say is best practice, and we can put it in the black box. We can put it in the label.

I think the distinction is recommend versus require. I think require is too strong if we talk about this because it would require an unnecessary burden every, single month when someone's trying to get their refill. Adherence was already poor here, and going to a requirement that someone be proven HIV-negative, not only to start -- but the pharmacy's not going to make a distinction between start and continuation. So basically, it means an HIV test every single month. I think that's going overboard. That's going to be a barrier.

DR. FEINBERG: Well, the study's tested monthly. I think what's up for discussion here is what is the appropriate repetitive interval for testing.

DR. GIORDANO: But pills are typically dispensed at 30-month intervals. So -- I'm sorry, 30-day intervals. So if we do a 30-day supply, that automatically implies a 30-day repeat HIV

test.

DR. FEINBERG: Well, let's just say the panel says that every 90 days is a reasonable interval for testing. Then the prescription is 30 days and two refills. I think there are ways around that.

I guess the other piece of perspective I have is that I am on my state's ADAP board, and I see the prescription data. And this was before PrEP was even on the table. And I will tell you that there are physicians prescribing monotherapy and dual therapy in the world. Okay?

So I think our assumption that everybody is at the standard of care is not a safe assumption. And presumably, these are people writing prescriptions for people with HIV, so they presumably have some something going for them.

So I'm a little anxious that the people around this table are all really the creme de la creme, and the 200,000 people out there writing prescriptions are -- it's a very different set of circumstances. So I'm perfectly comfortable with

saying, you should have a negative HIV test before you get these drugs, because the harm is huge, and then you seroconvert and you become resistant, and you don't know you're HIV-positive, and you've got viral loads of millions, and you go out and infect another 10 people. And how you're not only infecting other people, but you're giving them a K65R and M184V virus.

So I think we should really think about that part carefully.

Dr. Hunsicker, Mr. Sharp, Dr. Vega

DR. HUNSICKER: I'm a relative amateur in here in that I'm basically a transplant doctor. But I've listened to this, and I think that the sense that I get from both the community and from some of the other discussion is that to make this a requirement at this point would be an extreme burden. Nonetheless, I share your concern that there's real risk out there.

I would just like to make the point, we don't have to make a final determination forever right now. One of the possibilities is to say,

let's start with the relatively open system where we put all the black boxes and all that stuff in place, and then see what in fact happens. And if we find that there is an excessive amount of risky behavior -- and let me tell you, I agree with you; people do stupid things even though they're perfectly informed. If we find that there is an excessive risk, and if we find that that excessive risk is associated with emergence of resistance, we can change the rules in two or three years.

I think that to try to put this in place today would lead to more damage in terms of not making it available to people who need it, and possibly throwing up barriers to the people who are already infected, which is the other issue here, than can be justified by our worry about what happens.

But I just want to reiterate that we don't have to stay ignorant forever once we make that decision. We can change our mind if the data suggests that there's a real problem.

I wanted to suggest one specific thing with

respect to evaluating. There's a problem with the voluntary registry that everybody does voluntary registries knows, that both at the doctor level and at the patient level, the people who will not volunteer to be in the registry are the people for whom the risk of noncompliance is going to be the greatest.

So there really is a necessity to develop a mechanism to look for unwise behavior, if you will, amongst the people who are not volunteering to be in the registry. I would just like to suggest it may be possible, since a disproportionate number of these people will be in the Medicaid program, to look at the frequency with which Truvada is being prescribed in the absence of a second drug and in the absence of repeated monthly testing. That is something that could be done and might, in fact, clarify the rate of stupidity in the doctor population.

DR. FEINBERG: I think we're going to do Sharp, Vega, Wood, Morrato, and Padian, and then Blower. We'll do the best we can.

MR. SHARP: So I'm not on the side of restricting access at all to this for PrEP. But I wondered if anybody -- maybe the FDA knows about false prescriptions because I think that could be an issue, people writing false prescriptions. And that would get through any kind of testing requirements. It happens.

DR. VEGA: You read my mind.

MR. SHARP: I don't know how much, but --

DR. VEGA: You read my mind.

DR. FEINBERG: It's your turn, Dr. Vega.

DR. VEGA: Oh, great, because I'm busting. Okay. False prescriptions? Okay. You can go on any street corner in the South Bronx, and for anything from 1.50 to $5, I can tell you a variety of drugs that you can get.

If we're the creme de la creme, okay, and I thank you so much, allow me to say that our patients are the creme de la creme to the third power. I think that we should not underestimate the ability to get over. And by that I mean that we have very resourceful patients who often are,

shall we say, drug-takers and sellers and all kinds. And they have a wonderful street sense. They have a wonderful ability, a facility, to not go to one physician but to go to several physicians and to have several family members -- de la Vega, de la Lopez -- okay?

I'm not Ricky and Lucy now, but what I'm suggesting is, okay, that we should not underestimate the power of somebody who chooses to be involved for the sake of really, really, truly wanting to get better or wanting to prevent something.

I'm a three-time survivor of cancer, and I wanted desperately to live, unlike everybody else in my family who had passed from cancer, so that my kids wouldn't be -- my daughters abandoned. And there were still times, though, to speak on the other side, that I forgot to take my chemo. And my unconscious forgetting was very clear because the symptoms were so severe that I really wanted to die at some point.

So I think you have two sides, at least,

perhaps many more. But being a senior resident of this panel, very senior today, I'd like to say that we should -- I think everybody here really has a really good feeling about wanting to help people. I mean, that really seems to be -- and Madam Chair, you know how to keep them to three minutes. It really has been a very productive time. And many times when I said, I'm never going to last these hours, we were able to. And I think that's because of the real, real strong feeling here that people have for the consonance in wanting to survive. But also, I think we have to be very careful that the people that we're dealing with may have very mixed, ambivalent feelings, and sometimes they show themselves in some very interesting kinds of ways. Thank you.

DR. MURRAY: I think this might constitute the discussion of question 3. But I think maybe we have to vote, considering the REMS is the way it is, is that. SO you can vote yes or no and then explain your vote later. And if it is no because it's not a restricted distribution REMS, then

that's fine.

The thing is, is that in these times when government is supposed to shrink, apparently, there's just no mechanism for monitoring physicians testing for HIV in kind of an easy way. There's just no real resource or agency or organization that's able to do that without setting up a lot of barriers.

So I think we're kind of left with strong education. You brought up for treatment, people are using this wrong for treatment. Then I would ask, well, why don't we have restricted distribution for treatment if people are using this as monotherapy and dual therapy, and making sure that a physician attests to that I have passed this test in HIV care or something.

So that's what we're talking about that reaches a level to ETASU, something that can be validated by a physician's attestation, or they have to have passed certain tests and somebody has to monitor that they've actually done these sort of things periodically.

I guess what we're saying is, there's no real way in what people are thinking about ETASUs to have that kind of restriction. Although we think that, yes, it is a requirement to use this drug to test, that there's no way to officially monitor it or enforce it under an ETASU.

DR. FEINBERG: Let me see if I understand this better because maybe this is coming through to me now. You're saying that if we use the word "must" or "require" or whatever, that that puts the onus on the agency to follow that up? Because, after all, once drugs are approved, healthcare providers can prescribe whatever they like for whatever they like, and you don't monitor that.

So I'm just curious. You all seem very anxious that this is going to be an untenable position for the agency. And I'm wondering why, when most of the REMS is completely passive to begin with. How are we really in the end going to know anything about anything if we're just handing out pamphlets and asking doctors to click on the internet and say, did you read the pamphlet?

So I'm a little lost in this. Can you clarify that?

DR. MURRAY: We'll have Carolyn talk about it. But I know, I'm very fuzzy. I admit, I have a hard time understanding the legalese of the REMS and ETASUs, what they mean. But I think an ETASU is something that has to be monitored and assessed officially -- and Carolyn, you can go through the details about this -- not just, yes, physicians are required to do that; we're going to write this in the REMS. No, there's a whole -- assessments have to be made to ensure that physicians, yes, are doing that, and there's reports that we have 90 percent compliance with this, and all that.

DR. YANCEY: Carolyn Yancey, Food and Drug. Let me just go back to the first two slides that I presented, a background for a REMS, and something I often talk about in internal meetings.

We have the clinical program before us. We have the report of safety. What are the safety risks in that program that we believe rise to the level of a REMS that we also believe require more

risk mitigation than the labeling?

The labeling, absolutely, is very clear. It's not final and substantial. But it includes recommended monitoring. It includes screening. The items for screening that you've heard discussed today, in renal, bone, et cetera. So the risk of development of HIV drug-resistant variants is the area of risk that we felt required a REMS -- that is, mitigation and risk strategy beyond labeling.

One of the pieces that hasn't been commented on in this recent half-hour of discussion, which is excellent, is the way in which the agency has modified this proposed REMS to monitor it more carefully. The timetable for submission of assessments, as currently proposed, has been moved to 6 months, 12 months, and annually thereafter.

This REMS, as discussed internally and robustly discussed externally to the agency, will have very careful monitoring. The pharmacy vendor data, we are willing to look at that pharmacy vendor data at six months to see how difficult it is to identify Truvada prescriptions without

concomitant antiretroviral products.

So we have prospectively, if you will, teased apart different ways to get at information as early as possible. The applicant submitted in their proposal, certainly, their projected off-label use as it currently exists, and they can share that at this point if they like. It's very small.

But I think in terms of first round, if you will, of an assessment, it will be early. It will be at six months. Based on all the efficacy we heard, access is the key, is the platform, if you will, to the efficacy that's been reported. People have to have access to the product.

I think the points that have been brought up about monitoring are critical. The reason, if you look at what is proposed for prescriber training and education, there's a first component, and it's early dissemination of the safety information. We have asked the applicant to provide us with their proposal for two to three organizations that they believe will reach likely prescribers for Truvada

for this proposed indication, and that is purely to disseminate safety risk information early, twice a year. And we're considering that for possibly a two-year initiative.

DR. PADIAN: But is the assessment -- I love that it's early; it's great. And I love Dr. Hunsicker's point, which I think -- if it weren't strictly voluntary, that it was somehow representative of what was going on, I think a lot of -- certainly my concerns might be allayed.

Because I think Dr. Feinberg put it so well. This is sort of toothless. And I don't know. I don't work for the FDA. What are the various ways we can give it teeth and that we can make sure that we can get good data about what's going on? And I would vote for not a voluntary assessment.

DR. YANCEY: If you go back to slide 6, elements to assure safe use, FDAAA, if you will, gave teeth to the agency and what could be required based on safety information.

The fact that Truvada, the moiety, is approved, available on the market, any combination,

if you will, of restricted elements to assure safe use that would be linked to restriction -- that is, a hard stop for the patient to receive a prescription -- could be circumvented.

DR. FEINBERG: I guess what I will say to all this, if you go to slide number 132 from the sponsor that talks about what they're going to do in the proposed REMS, it is completely passive. Completely.

Going to send a notification letter, a "Dear Healthcare Provider" letter. Going to send them the prescribing information. People get this stuff every day, round file it. It's another prescribing circular. A medication guide with every bottle of Truvada. That's good for the patients. A training guide for healthcare providers. Safety brochure for the prescribers. Safety brochure for the individual -- it's completely passive.

Then when you look at the FDA version on your slide number 6, elements of a REMS, and it says, elements to assure safe use, the ETASU slide, we're talking about ABCDEF.

Everyone at the FDA side is saying, we're happy with A. "Healthcare providers who prescribe the drug have particular training or experience or specially certified." Well, the proposal is clearly not to assure that people are specifically certified. The proposal from the sponsor is utterly passive.

So the slippage between their plan and ETASU A that everyone seems to be happy with, but you're unhappy with proposals from the panel, ETASU D, that it be dispensed to patients with evidence of safe use -- and I would say also E, certain monitoring -- I wouldn't want to prescribe this for somebody who had a creatinine of 3. I would want to do a renal panel before they get this drug.

Dr. Birnkrant is nodding her head yes, because this is standard of care.

DR. BIRNKRANT: Right.

DR. FEINBERG: It's standard of care if you're an HIV provider and you know what you're doing. It is not standard of care for 200,000 Ish

Kabibble healthcare providers in this universe.

(Laughter.)

DR. FEINBERG: I think the potential for us to do harm by the 200,000 is clear.

DR. BIRNKRANT: Okay. We hear you, loudly and clearly. But the question back to you, before we get to the vote, is, how can we do what you want without restricting access to those who need it for treatment?

DR. FEINBERG: Since I was so heated, I'll at least answer that, and then I'll let the rest of the panel.

I think that not only the label but the REMS, that is the passive carrier of the information, should educate people and say, you should not prescribe this drug for somebody until you know whether they have HIV or not. We still have to argue about how do you define that. Right? Because there's antigen, antibody --

DR. BIRNKRANT: Right.

DR. FEINBERG: -- combined antigen/antibody, viral load. There's a lot of different ways to

look at that. And that will at least, to the extent that the passive receipt of information where somebody actually looks at the label, will at least make sure that the people for whom this isn't bread and butter, everyday medical practice, pay some attention to that.

You're not certifying people. You're not asking them if they passed a test. So I don't see with you the agency feels like any -- there's no way you're going to know whether doctors do this test or not. As I said before, lawyers will figure that out, and then doctors will change their behavior.

But I don't see how that gets in the way. And I think it augurs for better medical care and reduces risk. I think we're all about the do no harm part. Dr. Hunsicker -- oh, no. Dr. Blower had her hand up a million times ago.

DR. BLOWER: Well, this relates to the risk. How are you going to actually monitor it or have any idea what resistance is arising? Because there's nothing in the REMS about that, and it's an

incredibly difficult thing to do.

DR. MARCUS: I'm just going to back up one comment. I understand the concern about wanting to document a negative test. But if that is made a requirement of the ETASU, then the sponsor will have to make an assessment as to whether the requirements are being followed and if the requirements are mitigating the risk.

So what I'd like to ask is, how are prescriptions for Truvada going to be identified as prescriptions for PrEP? How are physicians who have written prescriptions for PrEP going to be identified? And how are the negative tests going to be verified that they have been collected prior to distribution of a prescription for Truvada?

Now, I understand that the idea is that lawyers will do the enforcing. But the reality is that FDA has to enforce, and the sponsor has to implement, and the sponsor has to assess. So I am at a loss as to how each piece of that will be achieved.

In particular, if the point is to ensure

that an HIV test has been documented as negative before a person gets a prescription for Truvada, where's the enforcement when a patient goes to a pharmacy with a prescription for Truvada? How is that going to be flagged as a prescription for PrEP and not for HIV in order that the physician can be identified and the HIV test verified?

DR. FEINBERG: How were you going to do it anyway? How was anybody going to look at the prescription volume for Truvada and decide what is PrEP and what isn't? I don't see how having the test gets in your way of doing that at all.

DR. MARCUS: It gets in the way of enforcement and assessment, creating a system whereby the prescription for PrEP can be identified, the physician who has written the prescription can be identified, such that the HIV test can be verified. That has to be done if it's a requirement.

DR. FEINBERG: All right. We should let other people speak. Dr. Morrato?

DR. BLOWER: I don't think you answered the

resistance question.

DR. MARCUS: Can you repeat the question?

DR. BLOWER: Yes. How were you going to monitor resistance? Because you didn't mention anything in the REMS, and it's an incredibly hard thing to do.

DR. MARCUS: I think that perhaps Gilead can address that question. I think from, our side, the thought is that that can be evaluated in a demonstration project, where you have people within the context of a study or a trial converting.

DR. BLOWER: But then ethically, you have to take them off as quickly as possible. So you wouldn't be able to find resistance.

DR. FEINBERG: Did somebody from Gilead want to address that?

DR. ROONEY: Hi. I'm Jim Rooney, vice president of medical affairs at Gilead Sciences. We have a variety of demonstration projects that are ongoing that were mentioned earlier in the presentation. Many of these are actually assessing resistance. And in a moment, hopefully, we'll have

a slide up. Yes, please. Slide up.

So there are a variety of demonstration projects that are either planned or ongoing that are going to be evaluating resistance. This is a list of the slides that will be evaluating in the context of studies for MSM.

As you can see, there's a large number of studies that are planned here, with over 12,000 subjects involved in MSMs. And if we could have the slide on heterosexuals as well, please. Yes. Slide up. Great. Thanks.

So there also are a variety of studies ongoing that will also be assessing resistance, and these will be done both in the U.S. and internationally. So in the context of these trials, we hope to gain substantial additional information in terms of the development of resistance.

Many of these demonstration projects will be administering -- as you know, in the clinical trials we've seen today, HIV testing has been done on intervals from every month to every three

months. In the demonstration projects here, they'll be exploring a variety of different testing intervals. So we'll be able to assess the development of resistance in the context of those as well.

DR. BLOWER: Can I ask what testing intervals? What are the longest testing intervals you're going to do?

DR. ROONEY: The majority of the studies here are evaluating every three months. There are some proposals to extend that to every six months as well.

DR. FEINBERG: Dr. Morrato?

DR. MORRATO: Yes. This is Elaine Morrato. I appreciate that no one wants to have a restrictive access. All right? But I do want to share some learning that came out of the isotretinoin.

So this started in the 1980s, and it was labeled category X, or pregnancy X category because it's a teratogenic risk. It was followed by strengthened labeling in the '80s, targeted

education, reminder tools, patient information consent forms, and patient and prescriber surveys to assess compliance with the program. Very similar to what we're hearing proposed. It was still not meeting the goal of minimizing fetal exposure.

It then turned into more of a SMART program, in which they're using yellow stickers. And it was going to prescribers verifying that this prescription has been checked over before the patient would go to the pharmacy system. That was labor-intensive, didn't work. But it still didn't meet the goal of minimizing fetal exposures.

It wasn't until the iPLEDGE program went into place, in which it had these -- ETASU, certification of the provider, linked with a patient registry, the physician registry, and linked with the pharmacy -- that you started to really get rates down. And even with all of that, you still have fetal exposure to the drug. Okay?

So I look at it and say, gee, how do we weigh the risks of fetal exposure in a teratogen

versus what we're talking here on resistance development. I know you can't compare apples and oranges, but to me, both seem very serious. And there are lessons to be learned that as you've said, Dr. Feinberg, that the passive way is just those tools do not work. They may raise awareness, but they're not necessary going to change behaviors.

So I think we could be more creative. And I understand when you have the same drug already on the market. But I guess what we're being asked is, don't approve it, and they can be prescribing it off-label; approving it with some things that we know won't be effective in changing behavior, all right, and we let it go that way, but now it's sort of certified as safe because it's been approved; or we try to maybe take another route in which we start restrictive and think of REMS in a way we think of stopping rules.

Not many REMS are thought and designed in a way to say, how would I step down REMS? What would I need to be collecting as I go into the product

launch such that three years later, I could lessen the REMS?

Could we think about it that way, such that it is started out first in sites that are treating HIV? It's not the 250,000 physicians in the United States that are going to get a pamphlet, but a more targeted approach. And we do do certification. Maybe we call it a separate -- I don't understand why we couldn't call it a separate product name. The physicians become registered so that they certify that they understand the pamphlet. The patients then are certified there, with the pharmacy, and we see how that rolls out.

There's been no data presented on what's happening right now with the CDC guidelines. If there were, maybe some of these questions would be answered, and that could be a first place to start.

But I just don't think it's a good logic to say, our choice is either don't approve and let them use it off-label, or approve it with something we know is not going to be very effective in actually changing behavior.

So I would argue we can think more creatively of trying to find out how to work the distribution systems. And the isotretinoin-containing products had to create a system by which they could verify the physician registry against the patient registry and the pharmacy. And it is cumbersome, and it is bothersome, and if dermatologists had a choice of voting about whether or not they'd want that system, they'd all say no, too.

So I think we just need to be consistent, also, as we look across different products and categories, and not set up systems in which they just don't seem to jibe with one another.

DR. FEINBERG: Mr. Raymond, then Dr. Glen, Dr. Strader -- oh, I'm sorry, I'm not on. Raymond, Glen, Strader, and then I'm going to put a proposal before you so we can see what we can do about this vote.

MR. RAYMOND: Thank you. I really believe everybody is talking in good faith. But I think the action that we ended up in the REMS discussion

before, actually having the indication discussion, is distorting some of this conversation.

I'm hearing things that express more concern about the possibility of acquired drug-resistant infection than the fact that we started today talking about how we have not moved the dial in over a decade on 50,000 new HIV infections a year, and there's got to be a balance there, that the less accessible, assuming that this indication is approved, this drug is -- if we start talking about patient registries, the people who are at most risk don't want to be on a registry. Right? If we can get them to connect to a healthcare provider in the first place, that's great. I mean, that's job number one.

But I just worry that this fear of drug resistance is so out of proportion to what the indication is actually meant to do, which is give a new tool as part of a comprehensive arsenal to prevent HIV infections, and move the dial, move the dial on that growing number of men who have sex with men who are newly infected each year; of the

50 percent increase between 2007 and 2010 of young black men who have sex with men getting infected each year.

I think everything that we should be talking about in terms of REMS, in terms of labeling, in terms of testing intervals and stuff, has to be seen in that context. And we haven't had that discussion yet because we haven't talked about whether we're voting in support of these indications. Thanks.

DR. GLEN: Yes. I'm actually uncomfortable with addressing at the level of labeling because I think, ultimately, the responsibility has to come back on the provider. Because they're not just going to be providing a prescription; it's a whole suite of counseling and other protective measures that has to be implemented.

I think the collective concern here is, what's going to happen in the real world with resistance, not in the context of studies. But that has to be answered with data. And so the question is getting comfort on how are we going to

get that data, and maybe just getting more granularity about the types of studies the sponsor's -- what we're starting to allude to is good.

I think the problem is studies are by definition, not going to be the real world situation. But how many patients are going to be in the studies? Where you are addressing longer, longer intervals of testing, which will give some real world assessment of what are actually the rates of resistance that will develop, and that will be a way of addressing the mechanism that Dr. Hunsicker was talking about. So I think maybe that would be one approach that could help.

DR. STRADER: I agree with the comments that were made. I think that the statement about the REMS that the FDA made is a little bit incongruous because if we believe that the risk of resistant infections requires a REMS in the first place, then we must put something in there that has, as she says, teeth in it. Otherwise, it is completely meaningless.

I can appreciate that the sponsors are planning lots of studies. But these studies are ongoing while we have, presumably, approved the drug that is being used but not necessarily being tested. We don't know who the physicians are that are giving it. The patients are registered. And I think it's a little bit dangerous to do.

I have a question that may be a little outside of the box. Is it possible to create an ICD-9 code for pre-exposure prophylaxis? Since we're breaking new ground here with respect to the treatment of HIV. So that would give us some way of identifying who's being treated for HIV and who's being treated for pre-exposure prophylaxis, and then would get rid of the issue about, well, how do we know that this isn't -- how do we prevent people who have HIV from not getting the drug? Because we don't want to give it to patients who have had a positive test.

DR. BIRNKRANT: Okay. Well, thank you for that comment.

How do you feel about taking a vote with the

thought that there will not be a restrictive REMS? And we'll just go with that at this point in time, based on the discussion we've had around the table. I meant restrictive distribution.

DR. FEINBERG: Well, I was going to propose sort of the flip side of that, which is that we could move to question 1 and vote on it, with the caveat that how we discuss questions 2, 3, and beyond will delineate how things work out.

DR. BIRNKRANT: Right. But once you take a vote, you've taken a vote, though. Right?

DR. PADIAN: With regard to what you said -- I'm sorry I can't see your nametag from here -- I'll speak for my own self. I wouldn't have this discussion about REMS if I didn't think this should go forward. Absolutely. It's been years. It matters so much. We've got to get it out there, in my opinion.

Well, you know my vote. This is transparent. So we have to do it the right way. So the reason why we're not having that discussion, for my own self, is because default, I agree with

that. And I really would be so sad if we couldn't do something that's a little bit more of a hybrid because it is so important. And I want to be able to approve this.

DR. FEINBERG: Dr. Murata?

DR. MURATA: I just have a clarification from the agency. I'm looking at the questions to the committee, and it starts with a vote and there are four issues for discussion, with a caveat that if the first one is a yes, then these are the things to be discussed.

So is it fair to say that -- the vote is, based on the data that have been discussed by the agency and the sponsor, is there a favorable benefit to risk ratio?

Then the points for discussion, 2 through 5, are -- and this is my interpretation, but I want to see what the agency would think about it -- are those further steps to more favorably increase the benefit to risk ratio? Is that fair to say?

DR. BIRNKRANT: I think that's a reasonable approach. But again, we have to be mindful of

question 3 and what we can actually do in the setting of a drug that's already approved.

DR. GLEN: So along those lines, maybe just a lot of this could be addressed by the answer to question 4 because it's really going to say what types of monitoring need to be implemented.

DR. FEINBERG: We could certainly, at the discussion level, swap 3 and 4. I don't see that that's a problem.

Dr. Cox?

DR. COX: Dr. Feinberg, thanks. I'm getting feedback here. I think the discussion reflects the complexity of the issues that we're dealing with here. And as I listen to the discussion, a number of the issues that I'm hearing described really do relate to question 2 and question 3.

I understand, with the first question, that people will think of that question in terms of what they might want to describe in questions 2 and 3. So perhaps one way -- and this is similar to what Dr. Murata is talking about -- is to look at question 1, especially evaluate that based upon

what your expectations would be for your subsequent answers in 2 and 3, you know, what other sort of steps with regards to medication would be involved in the testing and the follow-up intervals and such.

So that's one way, at least, to think about this. And maybe that will help a little bit because I think a lot of the discussion that's going on is relevant to those other questions. So obviously, your choice; but if you feel like we're at the point where we're ripe to move to the question, we certainly could, and then try and incorporate those additional thoughts as we move to questions 2 and 3.

DR. FEINBERG: Okay. So is the panel comfortable with that? Let me see if I can summarize what Dr. Cox said.

We'll move to question 1, where the wording talks about favorable risk/benefit assessment based on all the data we've seen today. And then we will address the other questions, and that will help the agency figure out the way to best ensure patient

safety In other words, because this --

DR. COX: It would be making recommendations with regards to question 2 and 3. So if there are certain elements that you think would be part of the program that you want to describe in questions 2 and 3 that in essence was part of your consideration as you were looking at 1, 2 and 3 would be the opportunity to provide some additional advice on the elements of the program.

Does that sound like a possible way to try and capture all the rich discussion on this topic?

DR. FEINBERG: Okay. If there's not a huge hue and cry after that, then we'll act on Dr. Cox's proposal. Let me read you the instructions about voting.

These little black boxes, your voting is underneath the button you press to speak. So this is an electronic voting system, and the advantage of it is that everybody votes simultaneously as opposed to sequentially, so there's no influence on hearing other people's votes.

Once we begin the vote, you'll see these

buttons start flashing. And they'll continue to flash even after you've entered your vote. Don't freak out about that. Press the button firmly that corresponds to your vote. You've got a "Yes," "No," and "Abstain." Okay? For those of you who are permitted to vote. I think it's everyone at the table except Dr. Robinson.

If you are unsure of your vote or you want to change your vote, you can press the corresponding button for the change until the vote is closed. So if your finger hits the wrong button, you can still correct that.

The vote would then be displayed on the screen, and then the designated federal officer will read the vote from the screen into the record. And then subsequently, we'll go around the room, and everybody who voted will state their name and their vote into the record so there's a verbal record of how the vote went.

You can also state the reason why you voted as you did, if you want to. And I would say, in the interest of our not being here till midnight,

if someone else has already stated your reasons, then just pass. I know we're all brilliant academicians, but sometimes you just need to not have to speak extra.

(Laughter.)

DR. BIRNKRANT: And the other thing is maybe you can explain your reasoning after you vote for A, B, and C.

DR. FEINBERG: Yes. We're going to do A, B, and C, and then we'll explain.

So the question I have -- let me read question number 1. And let me make sure that everybody at the table's comfortable with what this question means, because I had a question before. And it says, "Does the current application support a favorable risk/benefit assessment adequate to approve Truvada for a PrEP indication in:

"A. HIV-uninfected men who have sex with men;

"B. HIV-uninfected partners in serodiscordant couples;

"C. Other individuals at risk for acquiring

HIV through sexual activity."

Now, does C seem unclear or vague to some people? Because we could get clarification from the agency on that. It seemed a little unclear to me.

Dr. Ellenberg?

DR. ELLENBERG: A question I've been trying to ask and have not been able to ask, which is my concern about the VOICE study, which gave a very discrepant result with the Partners PrEP study. And that, to me -- it's the women who were at high risk in the VOICE study is what's confusing me about my possible answer to this question.

I would have liked to have gotten some feedback about what people's speculation is about those differences. But that's who I would read, as in that last --

DR. FEINBERG: My interpretation of this, and then I'll let the agency follow up, is that Partners PrEP was really a study designed in serodiscordant couples, which is how B is described, whereas VOICE is really a study of women

who may or may not be in a specific relationship or a discordant relationship.

DR. ELLENBERG: But in one of them, tenofovir was highly effective, and in the other one, it was stopped early because it had no effect. And so I would have liked to have heard something about why people think that's the case.

DR. DASKALAKIS: A quick question just related to that. Sorry. So if we say yes to approving the drug, again looking at the regulatory issue, there's no way that someone who's going to a pharmacy is going to say, "And my partner's positive."

So in other words, it almost becomes a moot point. You're just approving it for sexual prevention rather than for the details of that prevention.

In the study perspective, you can really limit the pool. But if a woman or a man goes to a pharmacy and says, "I have a scrip for Truvada," they're not going to say, "Here's my HIV-negative test, oh, and here's a picture of my partner and

his HIV test." So I think it's really hard to restrict it beyond.

DR. FEINBERG: No. No, because I think we're talking about the same thing, is that there was a sense that we did not want to be that restrictive, that we didn't -- or at least many of the people at the table did think that the pharmacist needs a piece of paper at all other than a valid prescription.

DR. DASKALAKIS: My point there really is that I think if one were to say yes to A and B, C is automatically a yes because there's no way to enforce -- I mean, what is --

DR. FEINBERG: Well, C, for example, "Other individuals at risk," could this be injection drug users? I mean --

DR. DASKALAKIS: For sexual activity, though.

DR. FEINBERG: I know. But they have sex, too, last I looked.

DR. MURRAY: It is acquiring HIV through sexual activity. So yes, some people might have IV

drug use in any of these categories. So it's just about how restrictive, the indication in the labeling.

Technically, the studies that we reviewed were done in MSM and serodiscordant, although TDF2 was not just serodiscordant. So C just meant all heterosexuals at high risk, either by their self-admission, demographics, previous STIs. It's basically the same act in B and C, except that they're not serodiscordant couples. They are perceived to be a high risk for other factors, which a physician and patient would delineate.

DR. FEINBERG: Sex workers.

DR. MURRAY: Yes.

MR. RAYMOND: So just to clarify, or make sure I'm clear, to me the relevance of those separate indications is actually about what goes in the label, what can go in the marketing, and all of that.

If you only choose -- if you don't choose all of them, then you're making a particular treatment about how this drug gets out there in the

world, even recognizing that it could be prescribed off-label, et cetera, et cetera. But all of the official information will say specifically, population X, population Y, not population Z.

DR. FEINBERG: Right. I think so. And I think to answer Dr. Ellenberg's question or to make a comment on it is, there is clearly uncertainty about what it means to have these studies with conflicting results. And in this moment in time, I don't see -- there doesn't seem to be a way to resolve those conflicts. And so it's an imperfect package. And I think what we're being asked to do is to look at the data that exist and say, overall, is this a better idea than not?

But many people have brought that up, and it was in the published comments from the public, too. There is not concordance amongst these studies, and at the moment, we just have to live with that. I don't know what else we can do with it.

Dr. Cheever?

DR. CHEEVER: Can I just ask a question? So in A, we say HIV-uninfected men who have sex with

men. But in fact, the study was -- they were really high-risk MSM.

DR. FEINBERG: Right.

DR. CHEEVER: It wasn't all MSM.

DR. FEINBERG: Right.

DR. CHEEVER: And here we're just talking about MSM in general. And then HIV-uninfected partners of serodiscordant couples, that's a really high-risk situation that they're in. And the last one is, I think, a completely mushy category based on some of the studies that we've talked about today.

But for the first one, how come we're not saying HIV-uninfected men who have sex with men who are engaged in high-risk behavior? I mean, why isn't that part of it since that was what the study was in? And thinking about risk/benefit analysis, that would be important.

DR. MURRAY: That's what's intended. Clearly, if you target a not-high-risk patient population, you'll get all toxicity and no benefits. So it has to be somebody who's

reasonably at risk, even for MSM.

DR. CHEEVER: Okay. But that's --

DR. MURRAY: If it's in MSM who's not having any sex, then of course you wouldn't give Truvada.

DR. FEINBERG: Are we ready? I don't know where the -- we haven't started the vote yet. So I did read the question, but I'll read it again.

"Does the current application support a favorable risk/benefit assessment adequate to approve Truvada for a PrEP indication in:

"A. HIV-uninfected men who have sex with men;

"B. HIV-uninfected partners in serodiscordant couples;

"C. Other individuals at risk for acquiring HIV through sexual activity."

DR. STRADER: We're voting on all of those at once?

DR. FEINBERG: No. We're going to do one at a time. But I was just reading you the whole thing. So we're going to vote A, then B, then C.

Okay. So we are first now voting on 1-A.

(Vote taken.)

DR. WAPLES: For the record, there is 19 yes, 3 no, zero abstain.

DR. FEINBERG: Okay. Now we're going to vote on 1-B, HIV-uninfected partners in serodiscordant couples.

DR. WAPLES: For 1-A, we need to go around the tables --

DR. FEINBERG: Oh, I'm sorry.

DR. WAPLES: -- with stating your name and the reason why you voted as you did before we move on to --

DR. FEINBERG: Let's do all three and then go around.

DR. WAPLES: I apologize. For our voting system, we will need to move through. Let's get through with 1-A and move on to --

DR. MURRAY: It would make it much faster to do it after all three. I don't see much difference. You'll address A, B, and C at once. But then we'll be going around this table of 25 people three times, and we can go around it once

for A, B, and C. And we'll be able to break it out and still have all your answers you need, I think.

DR. PADIAN: I second that.

(Laughter.)

DR. FEINBERG: As we go around, I think, as Dr. Murray just said, you can say, "Yes, no, yes," or whatever your three votes were. But you're right. If we take comments three times, we'll be here till 6:00 a.m.

Okay. I appreciate everyone's tenacity and durability. This is almost like an antiretroviral regimen.

DR. WAPLES: Okay. We can answer all three, A, B, and C, at this time. When we go around the table, each person will have to say 1A, how you voted; 1B, how you voted; 1C, how you voted. You have to remember how you voted for each of those, A, B, and C.

(Laughter.)

DR. WAPLES: I will not have that. Okay? So we can do it that way.

DR. FEINBERG: Hopefully people have that

much IQ here.

All right. Now we're going to vote on 1-B, HIV-uninfected partners in serodiscordant couples.

(Vote taken.)

DR. WAPLES: Two votes are missing. Please press your answer in.

DR. FEINBERG: All right. Everyone revote. You want everyone to revote, then?

DR. WAPLES: Yes, please.

(Vote taken again.)

DR. FEINBERG: Do you have all the votes?

DR. WAPLES: For the record, we have 19 yes, 2 no, 1 abstain for 1-B.

DR. FEINBERG: All right. Now we're going to vote 1C, other individuals at risk for acquiring HIV through sexual activity. Ready? Go.

(Vote taken.)

DR. WAPLES: We're missing one vote at this time.

DR. FEINBERG: So we have to do it again?

DR. WAPLES: Please press your button again for -- everything's up? Okay.

For 1C, the results are 12 yes, 8 no, 2 abstain.

DR. FEINBERG: Okay. Dr. Ruiz, you're up.

DR. RUIZ: All three? For all three, Correct?

DR. FEINBERG: Yes.

DR. RUIZ: Okay. I voted yes for 1A, yes for 1B, and yes for 1C.

DR. FEINBERG: And state your name for the oral record.

DR. RUIZ: My name is Monica Ruiz.

DR. FEINBERG: Good. Okay. Dr. Padian?

DR. PADIAN: My name is Nancy Padian, and I voted yes for all three, for the reasons that we discussed before, which is I think making the distinction that once you vote yes in principle, I think it's a murky decision between them or among them, I should say; but also, contingent on, for me, what is a very important bit, that we can in fact change the REMS, the monitoring, call it what you will. And I will feel duped if we can't.

DR. CHEEVER: This is Laura Cheever. I

voted yes for 1A, yes for 1B, and no for 1C. For A and B, I did because I think there's excellent data and we need to be moving that dial, as we discussed.

For 1C, I think that some of the contradictory data from some of the studies seemed to look like low adherence, and people may not consider themselves at risk. And so I'm not really sure what these other individuals are and how much risk they think they have. And if they're being prescribed a pill, and people think they're being safe, and in fact they're not. And it's a null impact, that they should be given the drug, and that we need to understand that better before we have that indication.

DR. KUHAR: Hi. David Kuhar. For 1A, I voted yes, for 1B, I voted yes, and for 1C, I abstained. For 1A and B I voted yes for reasons already stated.

Abstention? Well, and I abstained on 1C in many ways for many reasons that Dr. Cheever just stated. But I felt unclear on how risk assessment

would be done in the rest of the population.

DR. GIORDANO: My name is Tom Giordano. I voted yes for 1A, yes for 1B, yes for 1C. I believe there are strong efficacy data, strong animal model data for sexual transmission both in animals and men and women.

The trouble is adherence, but I don't think our charge is to judge whether people will take the medicine; I think our charge is to judge whether it can be -- whether it works, when it's taken, and whether the risks are outweighed by the benefits. And that's why I voted yes for all three.

DR. CORBETT: Amanda Corbett. I voted yes for 1A, yes for 1B, and no for 1C, mainly no for 1C for what's already been mentioned. I just feel there's not enough data in that population.

I voted for 1B equally as for 1A yes. I do feel there re differences and risks for women versus men, but I feel like it still should be labeled for both, serodiscordant as well as for MSM, in the good faith that there will be some excellent postmarketing surveillance and very

critical surveillance of this distribution of medications that's already been mentioned before.

DR. NEWCOMER: I'm Susan Newcomer. I voted yes for 1A, yes for 1B, yes for 1C, for the same reasons as Dr. Padian.

DR. BLOWER: I'm Sally Blower. I voted yes for 1A, yes for 1B, and yes for 1C, for the reason there's excluded data to approve PrEP. But like Nancy, I think it's essential that the REMS strategy is stronger to mitigate the potential of resistance.

DR. ELLENBERG: I'm Susan Ellenberg. I voted yes for 1A and abstained for B and C. I voted yes for 1A because I think the data from the two primary studies that we heard about were quite strong. But I'm concerned about this great discrepancy with this other study that seemed mostly to be relevant to the populations in B and C. And because the first two studies were really so strong, I couldn't bring myself to vote no. But I also couldn't bring myself to vote yes, so I abstained.

MR. RAYMOND: I'm Daniel Raymond. I voted yes for 1A, yes for 1B, yes for 1C, largely for reasons already stated.

I also wanted to acknowledge, in light of some of the comments from the public earlier, that my experience with this whole debate around PrEP over that year, year and a half or so, has been haunted by a certain specter of what I would characterize as maybe an undercurrent of anger and fear at people who don't or can't or won't use condoms, at people who don't or can't or won't adhere to medications, and then ultimately at people who don't care or think or live as much with HIV as so many of us do. And I think that that drives a lot of the assumptions about who these three subpopulations are, how they would behave, what they'd need, how to manage their behavior, how they manage their own behavior.

At a certain point, I think the other context for me, not just the last year and a half of discussions, keeping in mind that this is the 25th anniversary of the AIDS Coalition to Unleash

Power, and part of the legacy of that movement is really patient empowerment, really about learning and mastering the science and sharing it within our communities.

I think that PrEP gives us a new opportunity to do that all over again, and to do it just as responsibly as we've been trying to do for the last 25 years. Thank you.

DR. DASKALAKIS: Demetre Daskalakis. I voted yes on 1A, yes on 1B, and yes on 1C, for many of the same reasons. I feel like one of the important issues we've been asked to do is to look at the risks and the benefits of the intervention.

The preventive benefit of this is very high. The biological and social risks are, frankly, very low. So for all of these populations, it seems to make sense that we do approve this strategy as a concept, and then really work as a population of people who provide care to folks at risk to further fine-tune this very important tool so we'd learn how to implement it. So I voted yes so we can actually figure out how to make it happen, and make

it happen better.

I also want to second another comment, which is that prevention needs to be uncoupled from judgment of behavior. And so I feel like our goal, if it is to prevent HIV, it is not to judge what people do but to prevent HIV.

DR. GLEN: I'm Jeffrey Glen, and I voted yes on 1A, yes on 1B, yes on 1C, and especially because, again looking at the risk to benefit ratio, to me the benefit really -- the fact that it includes sparing some people a devastating disease, and also being contingent on being quite confident that, ultimately, the agency is well-suited to make sure that adequate prescribing and monitoring will be implemented.

DR. STRADER: Doris Strader. I voted no on 1A, yes on 1B, no on 1C, because I think that it's hard for me to uncouple adherence from efficacy. If we don't have sufficient adherence to a drug, it's hard for me to know what to make of the data if 40 percent of people may or may not adhere to the drug as it was prescribed.

So it was difficult for me to decide on the high-risk MSM population, and certainly on the FEM-PrEP population, which I believe they said was stopped early because the adherence was so poor, they could not make any judgments about whether it was effective or not. So I felt very uncomfortable with respect to 1C, about making a yes vote.

I would like to echo some of the comments made by two of my colleagues, to separate judgment from the votes that were made. But I also believe that we should not be cavalier, and that we should try to make sure that we have instruments in place to make sure that we are not, in our zeal to try to find something new, potentially placing patients at undue risk.

So I think that for me, this was one of the hardest things I've ever had to do, to try to balance those votes. And hopefully, I did it reasonably well.

DR. FEINBERG: Judith Feinberg. I voted yes on 1A, yes on 1B, yes on 1C, for pretty much the reasons that my colleagues stated. I think that

much needs to and must be learned about this. We're clearly at the baby steps. And so I have every anticipation that the sponsor and the agency will ensure, and we'll have a discussion about that shortly, that there's adequate postmarketing studies as well as surveillance and demonstration projects that we can really begin to finesse this.

It is, as Dr. Ellenberg pointed out, disconcerting that everything doesn't line up neatly. And I think by doing further studies, we'll figure that out.

DR. MURATA: I'm Yoshi Murata. I voted affirmatively to 1A and 1B based on the data and the analyses that were discussed today. I voted no to 1C. My feelings for doing that are in accord with those previously raised by Dr. Cheever.

DR. VAN DYKE: I'm Russell Van Dyke. I voted yes on A, yes on B with the provision that it really should be used as part of the full package of prevention, and therefore it should not be used for an uninfected woman with a positive partner who wants to become pregnant because I think the risk

of infection there is unknown but presumably substantial. And no for 3 because I think it really should be limited to a known positive partner. I do have concerns about the longer-term toxicity from this strategy.

DR. MORRATO: Yes. This is Elaine Morrato. I voted no on 1A, no on 1B, and no on 1C, because I believed that the risk management elements proposed were inadequate to ensure the safety and efficacy that was observed in the trials could be adequately translated into the real world.

I guess I'm from Missouri, the Show-Me State, so I wanted to see the details and how it evolved before voting yes. But if the questions that many have raised get resolved, then I could have voted yes as well.

DR. WOOD: Lauren Wood. I voted no on 1A, no on 1B, and no on 1C. The first reason for voting no on 1A -- and I think it's very important to let individuals know who came before during the public hearing to raise the issue and sensitivity and awareness to make sure that options, new

options and new options in the toolbox, were available for black MSM, was one of the major considerations. But I have significant safety concerns because it's well-known that African Americans have an extreme disproportionate risk for end-stage renal disease, chronic kidney disease, and dialysis.

This approval is based on data that was conducted in a total of 140 African American men for the MSM indication, 117 males from the iPrEx study and 23 males from the CDC study. I do not think that t hat is adequate when you are talking about the population that is most at risk that we are trying to target specifically. That was the highlight of our initial discussions, and that is how we provide the armamentarium to the populations in this country that are at greatest risk.

I believe that without greater safety data that directly involves the population in this country, that we are doing a disservice to allow a huge number of individuals to be exposed when there is clearly a population predisposition for the

major toxicity associated with this drug.

I voted 1B for serodiscordant couples because there is no data in any American women. The next higher population where we propose to be targeting our therapeutic interventions for, where the epidemic is exploding in this country, in rural areas, in urban areas, in the Mid-Atlantic and in the South, is in heterosexual black women. And I want to make the committee aware that there is not a single African American female in any one of the studies that has been put forward for approval. I think that's unacceptable, and that's why I voted no.

I voted no for 1C because I believe the data is ambivalent and discordant when it comes to other populations, particularly women. And given the fact that the standard is, when you have an intervention, that you are going to provide to individuals who are healthy, the first priority is to do no harm. The second issue is efficacy.

I have concerns about the risk/benefit, about doing no harm, and then when we talk about

the efficacy, I think the efficacy has to be consistent -- that criteria was not met, in my opinion -- and I think the magnitude of the efficacy has to be substantial.

My final reason for voting no on all three positions is the sponsor has said that their recommendation for strict adherence would be greater than 90 percent. But under optimum conditions for which the studies of these approval indications are based on, none of those studies met that condition. Not one. Not iPrEx. Not Partners PrEP. I can't recall off the top of my head about CDC 2323 [sic]. But the studies themselves conducted did not meet the sponsor's standard for efficacy.

So I believe that it is wrong to license a therapy where, under our optimal clinical trial conditions, the standards were not met, for what we are expecting providers and patients and healthcare advocates in the community to adhere to. Thank you.

DR. VEGA: I'm not going after that one.

I'm not telling you what I voted. I don't care if it's up there.

(Laughter.)

DR. VEGA: I voted on A, B, and C, yes.

DR. FEINBERG: Just say your name.

DR. VEGA: Oh, I'm sorry. Lucy Ricardo -- no, Marlena Vega. And I think you made some wonderful points, though. I appreciate what you said.

I have a different feeling, and that is that I promulgate and live on and advocate enlightenment, education, and advocacy. And to me, I think that at some point what you said, Daniel, is correct, as you, Demetre, that we have to take responsibility away from ourselves and say that patients have to accept responsibility on many levels.

I think that piece and the judgmental piece together -- and being a liberal, probably -- also have a lot to do with what I voted on. But I also think that some of the other things that were raised are very, very relevant.

MR. SHARP: Matt Sharp. I said yes on 1A, yes on 1B, and yes on 1C. I just want to say one thing that hasn't been said, I think and I hope, which is the reason I voted positively for all of these is not only because I believe in the evidence and the risk/benefit analysis, but I also really think this provides an amazing opportunity for turning the tide of the epidemic in terms of getting people tested, reducing STI infections, all of the things that we need to move on. Just like Daniel said, we need to turn this dial.

So that's the reason I really felt strongly, even though, as you go down the list, some of the populations, the data's not as strong. But to me, as somebody who's been living with HIV for 23 years, I'm tired of seeing the ongoing infection rate. And this, I hope, will add to the toolbox, which has been said too many times.

DR. HUNSICKER: Larry Hunsicker. I voted yes on A, yes on B, yes on C. I voted yes on C with a little bit of hesitancy because I think it's sort of a pig in a poke, but my thought was that if

this stuff is effective for people who are at high risk because they are engaged in male-to-male sex or because they're in discordant relationships, it should be effective for people are at risk for reasons.

But I think that that particular description of C needs to be fleshed out a little bit more, and I think that it would be irresponsible to publish it just the way it is now. It needs to be defined very clearly.

I want to make some general comments about -- first of all, about safety and efficacy. I think that the data suggests that this stuff is effective for the period of time of the studies, and I think that it is safe for the period of time of the studies. But I want to comment that it seems to me that you're likely -- if you are given to male-to-male sex or if you're living in a stable discordant relationship, it is likely that your exposure is going to last a heck of a lot longer than three years. And I don't think we have any data on the safety in the longer haul, and it is

therefore very clear that we need further safety data about this -- and also, for that matter, efficacy data in the longer haul.

Now, this then gets to my last comment, which is that we have a classic issue here of the distinction between efficacy and effectiveness. Efficacy is what happens in a study. What we have seen is what happens in a study.

Does this apply to the real world? Well, you're never going to find out what is going to happen in the real world by looking at a study. You are always going to have selected populations. It's never going to apply to what you really are interested in. So it is essential that we look at the -- what's missing in our information is the effectiveness piece here.

Now, I'd like to make a comment because we have heard a lot about how condoms are 95 percent or almost 100 percent effective, whereas Truvada is only either 46 percent or 54 percent or whatever that is.

Now, I would like to suggest that if you're

looking at effectiveness, everybody who is having sex in a situation in which their risk should be considered to have had prescribed condoms, and yet clearly transmission continues to occur, compliance with condoms is nowhere close to 100 percent. And I not at all sure -- if you believe the argument, which I think has facial credibility but is not yet really solidly established -- that the reason that Truvada failed in the group that it failed in was because they were noncompliant.

If you accept that that is the case, I think that you could say that there is an argument that Truvada is just as effective as condoms in the real world because people don't use condoms, just like they aren't going to take Truvada. That's not the problem of the method that we're trying to use to protect them. That's human frailty. That sort of stuff can only really be evaluated in population-based, long-term studies. And those are essential that they be done.

One last thing. We'll get to the business about the requirements for -- what do you call

it -- the REMS. One aspect of the REMS is reporting requirements, and this can be required. This can be absolutely required of the sponsor, that there must be appropriate population-based studies. And those studies have to include not only the volunteers that get into it, but you're going to have to be very creative and find out what happens amongst those patients who have Truvada prescribed for them who are not in the volunteer things, perhaps using a mechanism such as I've suggested. But that clearly is going to have to be worked out.

DR. ESTRELLA: Hi. Michelle Estrella. I voted yes for 1A, yes for 1B, and no for 1C, mainly for the same reasons that have been voiced already by Dr. Cheever. And I'd also like to echo the same concerns in terms of postmarketing evaluation, especially with the disparities between clinical trials in terms of kidney toxicity as well as observational studies.

DR. FEINBERG: Okay. So now the hard part. Question 2 --

DR. COX: Dr. Feinberg, if I may?

DR. FEINBERG: Sure.

DR. COX: One thing, just in the interest of time, I think there's a lot of valuable still to be had on 2 and 3, but we're sort of running out of time.

The idea may be to do 2 and together, so that we go around the table once, and if people could have their comments crisply articulated, perhaps we can hear both about 2 and 3 simultaneously, and do that in one go-around on the table.

After we get done with 2 and 3, then we can assess where we are with regards to time and make a decision as to whether there's enough time to hear about 4. So if we can do 2 and 3, if that would be okay with you, we could try and group those two together.

DR. FEINBERG: Sounds good to me. Okay.

Let's start at this side this time. So Dr. Estrella, you get to opine.

I'm sorry. I'm supposed to read this. I'm

getting very tired. I apologize.

"2. Discuss laboratory testing during administration of Truvada for a PrEP indication. How frequently should HIV testing be recommended? What safety assessments should be recommended, and how frequently?" And,

"3. Please comment on the applicant's proposed risk evaluation and mitigation strategy, or REMS, prescriber education program, including appropriate target prescribers and what metrics could be considered in the REMS assessment in addition to prescriber and user surveys, number of prescribers trained, and drug usage data."

There you go.

DR. ESTRELLA: Okay. So I guess to address question 2A, I think at this point I think everyone agrees that a baseline HIV test of some form, whether it be antigen/antibodies that we've discussed, is necessary in terms of safety.

In terms of frequency of testing, I think there really is no data, just except based on the clinical trials, which were discussed here. And I

think it would be important to follow up on the outcomes of the more extended HIV testing with regards to concerns for resistance. At the very minimum, I guess it would be three months based on the studies at this point.

Which safety assessment should be recommended, and how frequently? I have a bit of a bias towards, actually, more frequent testing for renal toxicity, mainly based on the disparities between clinical trials in terms of the frequency of renal toxicity, which was low in clinical trials but higher in observational studies. And that could be at least baseline serum creatinine as well as urinalysis, and more frequent risk assessment in those with risk factors for kidney disease such as diabetes, hypertension, hepatitis C, and injection drug use.

For 3 -- let's see -- prescriber education program, including appropriate target. Prescribers, I think what's been discussed before in terms of the REMS being mainly passive and really not having strength to actually monitor the

efficacy of the risk mitigation. And I believe that there are probably ways to be creative in terms of having more safety monitoring with regards to that. Thank you.

DR. HUNSICKER: With respect to number 2, how frequently should HIV testing be recommended, I'm going to be unusually bashful and say I'm going to leave that to the HIV people.

However, I do want to say about the other safety testing that it is not clear to me that the testing for renal toxicity is optimal, and you're talking about a tubulopathy for which GFR and albuminuria are really probably going to be insensitive markers. And I should think that one of the things that the sponsor is going to have to look to is what is a better way to get early warning on this.

Low phosphate is a perfectly start. I think that you might want to consider getting, actually, nephelometric proteinuria rather than a dipstick. The dipstick only looks for albumin; the other looks for total proteinuria. You could look for

specific things like beta-2 microglobulin, which is a marker for tubular difficulties. Or you might think of some of the things that have been developed in the renal community; eNGAL is one of the possible things that gets released in the presence of renal damage.

But I think that to count on the principal things that we in the renal community talk about, which are GFR and proteinuria, when you're dealing with a tubulopathy is a little bit erratic or irrational. And so I don't have specific recommendations except you ought to address that issue.

With respect to the risk evaluation and mitigation strategy, I've already talked about this. But specifically what metrics should be considered in the REMS in addition to how many people you've trained and all of that kind of stuff, I think one of the real focuses in the REMS evaluation has to be how consistent is the way in which doctors who prescribe this medicine for this indication actually do what is supposed to be done.

And that's not something that is explicitly stated up there, and thee are ways of doing that both through the registries and some of the things I've talked about. But that's a very important issue.

The reason I would emphasize that is that the risk of noncompliance to the patient is all sorts of stuff, but that's the patient's decision. The problem is that there is a public risk to noncompliance in terms of the emergence of resistance. And we have to have a handle on that.

MR. SHARP: Okay. So on number 2, I think one of the things that I may have missed but that should be included here is urging people or -- I think this is part of the education component, but urging people to recognize if they suspect transmission, if they have a transmission seroconversion syndrome, or if they suspect that they may have had unsafe sexual activity, that they should get tested. So I'm sure that's in there somewhere. But otherwise, I would go by the CDC interim guidelines, which suggest every two months. But I would be okay with three months HIV frequency

in testing.

Safety assessments, I'm not an expert on the kidney parameters. But I would certainly think that that would be important, whichever ones are the most important. And then in regards to the REMS, you need to think about this more. People learn in different ways; you all know about adult learning. So it's not just reading a pamphlet. There's got to be a creativity, which Michelle said, in how we get the REMS across.

I don't know. Let's be creative about ways to do this. Trainings, I hope, will -- I mean, how are we going to -- one of my questions about trainings is, who's going to implement those trainings? Who's going to do the trainings? How are they going to be done, and so forth. So all of that needs to be considered.

Then the one last piece, I would say, in here is, as an additional strategy, a really effective social marketing campaign. And I know people kind of roll their eyes when you say that, but this is something that is going to be new, and

I think a social marketing campaign, whether it's a part of REMS or not, is going to be important for educating people, even if they're sitting on a subway and they see an ad. I think that's an important component to the overall risk mitigation. Sorry, I'm very tired.

DR. VEGA: Hi. Marlena Vega. In terms of frequency, I love the idea of the CDC regulation for every two months. I like the more frequent, the more intimate, the better, getting intimate with your provider, and I mean that in many ways.

It seems to me that treatment resistance -- and I'm not just talking about the visit; I'm talking about the psychological piece, the treatment resistance -- can be brought down considerably by coming in there and kvetching, complaining, about what you don't want to do. The best sessions always are when your patient doesn't want to come. And I think that you can pick up on all kinds of issues by having somebody there more frequently. And the more they don't want to come, the more you call them and have them call you.

I use a system called "Comadre," which means when patients don't want to come, I have someone in their community -- it's shame-based, guilt-based. I believe in guilt induction, not reduction. And I really feel that works well with minorities as well as with many people who have wonderful consciences. What it does, really, is it says, I can do it, you can do it. Let's see how we can do it together or mis-do it together.

Okay. In terms of number 2 -- we did the frequency. Right? Okay. And safety assessments. Okay. I think for number 3, I'd like to give an answer that I think is important. You talked about a marketing campaign. To me, the best sell, hard sell/soft sell, is testimonial.

That is to say, I'm a three-time survivor of breast cancer, and when I get up to speak, I'm not Dr. Vega. I'm Marlena, who has had everything removed and put back. And I think it's very important to say to people and to show people on the train, on the subway, wherever, that people can survive providing they take their life into their

hands and are responsible.

So the more that's out there -- a pamphlet goes into the circular file, whether it's in Spanish or English, whether the Spanish is on fifth-grade level or high school level. I think that's a misnomer. I think what you really have to be involved in is very aggressive. And when we talked about the passive thing with REMS, I don't like passivity in any regard. So forget the passivity, girls and boys, okay?

I really feel we have something great here that we can do, and I believe everybody has their head on. And there's a lot of passion in this room, and not just on that side of the rope, on this side as well, thank God. And I really believe that if we -- I don't want to say tweak this, because that's not -- but if we get out there and have people who go through the process, clients who go through it who have been compliant, that's our best sales. Thank you.

DR. WOOD: Lauren Wood. I would agree with, again, the reinforcement of the baseline HIV test.

In terms of the initial monitoring, I am for anywhere from two to four months. I would be happy with three to four months. I do think it needs to be a shorter interval initially, and then as experience is gained, that could potentially be liberalized.

Regarding the safety testing, again I defer to Dr. Hunsicker and the nephrologist. Implement the tests that are going to be sensitive to address the toxicities, the long-term toxicities, of concern, which will also involve significant provider education if you're going beyond a urine protein dipstick and the eGFR.

We have not mentioned bone mineral density. That is something that is also going to need to be measured and monitored at least, I think, every six months, and again, based on the data that's coming in from different studies.

In addition to the consistency of prescribers prescribing the regimen as part of the REMS monitoring, I think that somehow there's got to be monitoring for how patients are staying

engaged in PrEP. If a patient pursues PrEP and decides to take it, there's got to be some kind of way to capture who's staying on track and who's falling out, and if they're falling out, why they're falling out, so that there can be adjustments to the approaches to capture the populations that are necessary.

In addition to patient awareness of the seroconversion syndrome, again given the fact that non-HIV providers are going to be a major target, they are going to have the educated regarding acute conversion syndrome.

I do find it kind of ironic that there was a substantial number of acute HIV infections, and these were missed by HIV providers who were enrolling patients in these clinical trials because they thought patients had a cold or sinusitis or something else. So that clearly is going to be another area that needs to be reinforced. Thank you.

DR. MORRATO: Yes. Elaine Morrato. So with regard to question 2, I'm not going to add anything

more than what's already been said for the sake of time. So I'll focus on question 3. And I'd like to build upon the notion of using the CDC recommendations in terms of screening, but also to go to each of the recommendations that they had in terms of behavior.

So I pulled from it. You're supposed to document negative HIV status. They recommend prescriptions be written with no more than 90 days' supply; that provision of counseling and condoms occur; that there's follow-up HIV testing, as we're mentioning, for the duration of the drug treatment; and documentation of HIV status when discontinuing drug therapy.

I would anticipate these are the same kinds of things that would be n product labeling, too. But in terms of measures in postmarketing, you'd want to be able to assess each one of those, and did they happen or not. And they might require different data sources in order to do it. Some of it could be done, perhaps, via pharmacy claims kinds of data and some of it may require a

registry.

So I would then recommend that -- the sponsors had proposed a phase 4 observational study. I'd like some more teeth to make sure that that actually happens in a timely way, so I would recommend turning it into a postmarketing commitment study. And perhaps the same study could also be designed -- I don't know -- but to address the question of surveillance of resistance because I think that's another endpoint that needs to be evaluated.

I completely endorse the creative ideas of Drs. Vega and Sharp in terms of the social media and all of that. The diffusion of innovation theory, the tipping point, all talks about that mass media channels, like pamphlets and TV ads and that, are very good at raising knowledge. But it's the interpersonal communication that's needed to actually persuade behavior.

Can we be creative in how we might engage local community opinion leaders and advocates within the community that could serve as, you're

saying, one-on-one trainers, role models, navigators, whatever we may call it. But that's part of the integrated commercialization of this. It's just not a pamphlet.

I know that happens for marketing, so it's set up to do these things. Why don't we use this same system to help us with the safety aspects? So I'd like to see better integration with commercialization.

Then I think it's commendable that the sponsor mentioned that they were going to hand out vouchers for free HIV testing, vouchers for condoms. I'd like to see more clarity of how that's really going to happen and to what degree or what's the reach of that program, what proportion of folks are getting it. Because one of the values of the study was the people got that every month, and that wasn't a deterrent for behavior.

So I'd like to see full coverage, if I could wave my magic wand. I think it sounds like the sponsor is recommending the knowledge, attitude, and behavior surveys be moved up a REMS commitment.

I support that. I think that's important, not to just measure the process measures of handing out things, but are you enacting any change in knowledge?

I know stated intent is not predictive of behavior. But it's better than just measuring, I handed something out to someone. And I would love to see if there's a way that you could at least think about how we might get the HIV testing integrated better so that we could -- I still don't understand why we can't have something approaching or trying to approach what's done for the isotretinoin in terms of having some auction rate security, at least during the period of the launch that this is occurring while behaviors are being established with the introduction of the new drug.

Thank you.

DR. VAN DYKE: Yes. Russell Van Dyke. In terms of number 2, clearly baseline HIV testing is required. In the two studies represented, the actual prevalence of primary infection, acute infection, was really very small. So I don't think

you could justify doing RNA testing on everybody at entry. I think that would cause a delay. It would be expensive. So I think probably antibody testing and screening for symptoms of acute seroconversion syndrome, obviously, as part of that. But if that's negative, I would think antibody testing. That would allow you to do rapid antibody testing, and perhaps education and, in the best circumstances, even give the prescription in a single visit. So I think that gives you maximal flexibility.

How often to do antibody testing? Well, there's no data. The studies did it every month, which is clearly not going to work in the real world. Three months sounds reasonable, but I think we need to learn a lot more about the balance between the risk of resistance in the seroconverters and the interval between antibodies, or between antibody testing in follow-up.

I don't know. Three months sounds fine. Less than that -- three months is going to be difficult. And remember, these are healthy people.

So getting them into the doctor's office every three months is really going to be extremely difficult, I think. You probably need to use the prescription as the carrot to get them in. And then that runs the risk of poor adherence because they don't come in to get the prescription. So it's very complex.

In terms of safety assessments, I think a baseline assessment is probably necessary. I defer to our nephrologists about some kidney evaluation, but clearly that's important. Maybe liver function. Neutropenia is not seen in these studies so much, but some of the other studies it is -- now, clearly with other HIV medicines. But I would think a baseline CBC would be reasonable, and then some reasonable follow-up monitoring schedule.

I don't think we know enough about bone mineral density at this point to recommend DEXA scans routinely on everybody. I think that would be very expensive, and I think we need to learn a lot more about what happens longer. But I think we clearly need a longer-term follow-up, both in terms

of renal function and in terms of bone mineral density. So I think we need the postmarketing studies and the phase 4 studies that inform us on that.

In terms of number 3, I don't really have much to add except we're under more and more pressure to do QA studies to monitor ourselves, monitor our friends, monitor our enemies. Board certification requires you to do QA studies. Hospital privileges requires you to do it.

So I think that could be perhaps taken advantage of. A good QA project would be to look and see how often HIV testing is done before the PrEP is prescribed, that sort of thing. So I think there's a way of building into the systems that are evolving now for greater oversight in how we're practicing to build it in because, clearly, the FDA is not going to be able to monitor this.

DR. MURATA: Yoshi Murata. I'll make my comments brief.

With regard to number 2, I think Dr. Van Dyke and others have clearly stated it's a balance

between getting the requisite serology tests, hematological and renal parameters, in conjunction with the prescriptions. Its being a 4-month period, that's up to debate.

With regard to number 3, I want to echo the sentiments previously raised by my colleagues, especially about the acute HIV seroconversion, particularly if non-HIV providers are the target or comprise a portion of the targeted audience.

DR. FEINBERG: Okay. Judith Feinberg. I want to start with baseline testing. I think it's pretty clear that we need to monitor renal function and tubulopathy, so that you need appropriate baseline test site. Yield to Dr. Hunsicker in terms of talking about what the tests really are. I think, from an ID perspective, we rely on creatinine too much, and that's probably not sufficient.

I think we should know people's hepatitis B status before we give them this drug because if they take it inconsistently, they're going to have a really big problem. I understand that the

elements of Truvada are not FDA-approved for this indication, but the drug is widely used for chronic hepatitis B. So if we don't know if people have hepatitis B, I think that's an issue.

In terms of the right HIV test, I'm a little bit torn. I think Russ is right about the practicalities of it. But in an ideal world, I'd like to either see an antibody test and a viral load, like the third generation antibody test, or the fourth generation antigen/antibody test, which narrows the window to about 21 days, still not perfect, but as we talked about before, I think there's tremendous risk in giving inadequate therapy to people who are already infected.

So I think we really ought to go -- even though it's not easy, I think we ought to go the extra mile to really find out what's going on. And probably the most straightforward way to do it across the board is an antibody test and a viral load.

With regard to how frequently HIV and safety assessments should be done, I would say probably,

in terms of practicality, something like on the order of every three months. To be honest with you, this I know is not the FDA's purview, but vis-a-vis all the other appropriate, impassioned comments about patients and patients at risk, you know, if people don't have to access healthcare, then how are they going to pay for a baseline HIV test, viral load, urinalysis, renal function, hepatitis B serology?

So I have a lot of anxiety about the people that we care so much about because they're at our highest risk. But I think our healthcare system is, unfortunately, organized against them. That's an editorial aside.

In terms of the REMS, I think I would go just a lot further than what was laid out here. And I think this is the bipartite. There's information that has to go to the patient -- actually, they're not sick so they're not really patients, but to the consumer -- and to the healthcare provider.

I agree that population-based studies are

1 going to be really useful in giving us appropriate
2 feedback about what needs to be done. But in terms
3 of prescriber education, I think, in addition -- I
4 really don't think passive things work very well.
5 I receive stuff all the time. You know, there's
6 just a lot of stuff you don't look at, and I'm not
7 sure that the busy internist or the business family
8 practice doc who gets a pamphlet about HIV pre-
9 exposure prophylaxis is going to pay any attention
10 to it. I think it'll be round filed.
11 So I think there needs to be more of an
12 active way to reach people. There's many ways to
13 do it. ACOG was fabulously successful as a
14 professional organization in getting obstetrician/
15 gynecologists to test so that we would limit
16 perinatal transmission, and it was fabulously
17 effective.
18 So I think part of what needs to be done
19 needs to be worked through professional societies
20 at the national level, at the state level, and
21 local medical societies. I think everybody
22 probably belongs to something, or most people

probably belong to something, the ANAC or whatever, or physician organizations.

So I think that needs to be done. And I think there needs to be grand rounds. I think there needs to be ways to get this info across that is not in the classic quote unquote "marketing" way so that the provision of continuing medical education, or for nurses, CEUs, that will entice people to listen would be a good idea.

So I think you can make a wonderfully academic presentation out of the terrific studies that we heard presented today and help get people to listen to it, because you're going to give them something that they need for their license renewal.

I think that when we about adherence, I think somebody mentioned prescriber adherence. So some of the follow-up studies, or at least the demonstration projects, do prescribers do any of these things? Do they get the baseline tests? Do they bring people back in? Do they talk to people about things?

I think that would be useful. And I think a

useful measure that we use all the time in enrolling people into clinical trials is we look for patient adherence, not so much the swallowing pills, but like do they show up for their clinical visits? If they don't show up for their clinic visits, the likelihood that they're going to show up for study visits isn't so great. And if we have some hesitation, we bring them in again and again and again. We say, we have to rescreen you. We have to rescreen you. And we rescreen them, and if they show up for all these visits, then they're probably a better prospect for being in a clinical trial.

So I think some of the follow-up has to be, do people come back for whom Truvada is prescribed? Do they show back up for repeat renal function surveillance? Do they come back for HIV tests? So I think there's two ways to look at those pieces of it.

In terms of the patient-directed thing, which I remember reading, said was going to be -- although this may not be totally what Gilead said

they would do, because this comes from the FDA booklet, it said, "A medication guide for uninfected individuals is to support education for PrEP indication about the serious risk of acquiring HIV and the subsequent development of resistance."

Well, I think there's so much more that a patient needs to know. And I think there's clever ways of -- all of the companies doing HIV have patient education materials. They all know how to reach patients, with pictures and words, and it doesn't matter what your reading level it. But I would say, you need the following important elements in the patient.

First of all, you need to talk to the patient about the need for monitoring. First of all, they need to know whether they have other -- HIV is just one sexually transmitted infection among many. So they need to understand that there's that aspect of it. They need to be monitored for potential toxicities.

I think you have to talk up front about the concept of Truvada as a party drug, or the risk of

sharing your prescription with other people who are not under a healthcare provider's care; if you share your drug with somebody who's got a creatinine of 3, guess what? So I think the people who are getting the prescription ought to -- it ought to be made clear to them that there's risk in sharing your drugs with your buddies.

I think the patient booklet should clearly talk about the continuation of other preventive measures; after all, the results on these studies were monthly intensive counseling and testing, which we all know isn't going to happen in the real world.

So up front, we should say that to patients, the fact that the effectiveness was completely dependent on adherence, or maybe the possibility I think that Lauren Wood raised of whether there's just different clearance.

I also think that it's important to talk to the patients about subsets that are a greater risk for problems with this drug. I think this should be shared with the docs, too, because they're not

all so smart.

But I think patients should really understand that there's a genetic risk for chronic kidney injury if you're African American, that people who already have kidney-affecting diseases like diabetes and hypertension could be at greater risk for this toxicity, so that people can at least self-identify, or think about it and at least understand that that's a part of the greater risk/benefit ratio.

I totally agree with this idea about social media. I think the social media can be used in many, many ways. If patients opt into it -- and face, it everybody under the age of 30 has one of these machines. I think if people opt into it, they can get reinforcement information over their cell phones. I think they can ask questions like, "I was sick to my stomach today. What should I do?" They're more likely to text it to somebody than to call their physician's office. So I think we should really think about how to exploit social media for reinforcement, appropriate education,

bilateral communication.

I think that's it for the moment.

DR. STRADER: Doris Strader. I don't think I have a whole lot to add to that with respect to question 2. I think that perhaps HIV RNA testing and antibody test is a good idea. I don't know about the interval. I would leave that to the infectious disease colleagues to decide. The same is true with the renal disease.

With respect to the REMS, I will be brief. The thing I feel most strongly about is that participation should probably not be voluntary. I think that prescribers should somehow be required to take some sort of training of some sort, that we should have monitoring that is necessary in order to prescribe these, and that some sort of safe use conditions should be documented. Perhaps it can be done via the electronic medical record in some way or something. And I'm sure that smarter people than myself can figure that out.

3C, additional strategies: "What additional strategies could be used to improve the REMS?" I'm

not sure if there's a possibility for having pharmacies involved such that we know how many prescriptions for Truvada they are prescribing in which community so we know which communities are getting pre-exposure prophylaxis.

But I think that there, as others have said, should be some very creative ways of using pharmacies and social media, electronic medical record, et cetera, so that if we are intending to use this drug, that we can be sure that it's being used appropriately.

DR. GLEN: Jeffrey Glen. I think, in my mind, the goal here is to mitigate the development of resistance and its subsequent spread, and the data presented really gives clear guidance on how to do that.

In terms of initial testing, the key is to avoid getting PrEP in the setting of an infection. In my mind, at a minimum, that means we need to test a viral load by RNA. The data shows that if you just look at an antibody test, you can be negative on entry; and even though the numbers were

small, those patients had a very high rate of becoming resistant.

Then in terms of subsequent monitoring, I would think, again, the data, at least as in the trials now, it's once a month. There an antibody was sufficient, and actually very impressively so, that if you follow people with the antibody, there was zero patients who developed resistance, even if they got infected on PrEP.

So that's how I would recommend it. It has to be monitored. And the hope would be with more time after approval and with more data, we could decrease that and see how things go in a real-world setting. But the data show that the longest time with a positive RNA or antibody was a month that you could treat somebody without testing.

Importantly, there needs to be an adequate mechanism to assess real world resistance on PrEP. And hopefully, the sponsors' studies that are already on the board that were outlined in the REMS will be sufficient. But this needs to be specifically looked at and determined that they're

adequately powered in real world settings and insufficiently representative populations, just to make sure that we'll get the data that's the most relevant and will give us guidance on how we can spread out testing to avoid the resistance.

DR. DASKALAKIS: Demetre Daskalakis from NYU. So first, on number 2, I agree with the comments about there being some combination of antigen/antibody or nucleic acid/antibody testing. I think that being very specific on that doesn't make sense because certain facilities will have different testing modalities available to themselves. As long as those two are in combination, I think that's reasonable.

I actually think that we should really pattern a lot of our frequency of safety assessments in HIV testing on the CDC guidelines for people who are at enhanced risk for HIV. So looking at the STI guidelines, they talk about testing at least once every three months, and I feel like that's probably a really good benchmark.

As the postmarketing studies get done, that

can always be changed. Like if it ends up that the data shows that two months is better, that's fine. But I think as a start, three months seems to make sense.

With that said, I also think it's an opportunity to say that part of the assessment of someone coming in for safety checks beyond their HIV status is also looking at other factors that potentially increase risk for HIV acquisition, which is to include that full battery of STI testing as part of the evaluation. Knowing that gonorrhea, chlamydia, and syphilis all do increase your risk for HIV acquisition, I think it's a reasonable safety gauge. And again, the CDC guidelines say that those, for instance, MSM at enhanced risk for HIV acquisition and other STIs ought to be tested more frequently, on the tenor of once every three to six months.

I agree with the fact that hepatitis B status needs to be included. From the perspective of renal assessment, I was looking at the idea of, say, guidelines, and they talk about doing at least

biannual, so once every two years doing a check of creatinine, phosphate, some sort of urine assessment of protein and glucose, and a BUN.

So I think it's reasonable to have that a bit more enhanced at the beginning, and merge that with the CDC tentative guidelines that say, zero to 3-month time frame, and then do it every 6 months from then on. So it's zero, 3, 6, 12, then every 6 months from then on, which would sort of be in synch in with what we say at the IDSA.

I also think that a couple of things that we've not talked about that needs to be assessed at least once every three to six months is the need for ongoing PrEP. So I think that it's important that we actually evaluate the patient in terms of risk, and I think that one of the deficiencies in the CDC guidelines and the deficiencies that will happen in practice is that we really don't have good tools to measure risk clinically.

So that may be something that postmarketing has to develop, something that's an easier questionnaire, something easy to do for risk to

decide whether or not someone needs to continue going on PrEP, realizing that providers are really poor at assessing sexual risk, sort of legendarily poor.

So I think that that's an important safety assessment, in my opinion, because if you don't need it, then you're safe because you should be off of it.

Going on to 3, I had an idea while I was sitting here about the prescriber education program, and thinking about how complex we're building this requirement for PrEP and what the provider side has to be, and the patient side. I mean, I was thinking that I barely want to do it, and I love the idea of PrEP, frankly.

So I wonder if we can look at the quality literature that we've been discussing and talk about checklists, and maybe think about having there be some sort of canned language that comes from the sponsor that can be used as, in effect, a contract between the patient and the provider that can go in the medical record that says, my job is

to assess you for this, and your job as the patient is to come in once every X months to get your HIV testing and your all of that.

So there's actually some sort of document, which is not binding, really, in any way except that it feels like a checklist. It also forces there to be a conversation between provider and patient to actually go over the expectations of what needs to happen for this ongoing relationship.

So it feels like it's from the quality literature because checklists really do seem to work for preventing mishaps. So I think that's a really good checklist.

In terms of the target prescribers, we haven't talked a lot about that. All of the target providers in the list seem to make a lot of sense to me except for one that sticks out, which is the ER. So I love ER doctors. I think that they're wonderful. But I think it's really important to make sure that the people who provide PrEP are people who have a longitudinal relationship with someone. And so that's a really important thing.

So that's why I made a big point about there's a separation between like what was in one document and the other. So I think ER doctors need to be educated, but they are not targeted providers, in my opinion.

The other issue on 3B is I really think that it's important to figure out a way to monitor resistance. I think that's been echoed a lot of ways. So I sort of then flashback to my own clinical practice and what happens when I have to fill out the paperwork for a trofile assay, which is a test looking for a tropism for HIV if one is going to start maraviroc.

On that form, there's a check box that says, "I am doing this because, A, I want to switch someone's meds because they are resistant and I want to see what their tropism is," or, "B, I'm going to initiate meds in someone naive and I want to see what their tropism is."

So I wonder if this is a great opportunity for the sponsor to talk to the couple of companies that actually do resistance testing and see if you

can throw a box on it that says, this person was on PrEP. And that way, with the relationship between the sponsor and that company, potentially, what an easy way to see who has resistance by just looking to see how many of the PrEP-checked boxes have mutations.

That's all I got.

MR. RAYMOND: Thanks. I really appreciate the thoughtfulness and the creativity and this dialogue that people are bringing to it, even when we've had disagreements about which indications are appropriate. And at such a late hour, I really feel people's presence here.

I would only say that I think that we're in this sort of phase because assuming that this introduction gets approved, the next 12 months are sort of going to be a bit of a laboratory. I think we'll have all kinds of different speculation and assumptions about what the demand's going to be, where the demand's going to come from, and who is going to be meeting that demand and who's going to be prescribing.

I don't think that picture will be really clear for a while. I think the enhanced pharmacovigilance that the sponsor proposes will help us to understand some of that. Some of the proposed demonstration studies and open label will help understand a little bit about what it looks like from the recipient's view, but I think this is all speculative. And with that in mind, I think you can take one or two approaches. Like during this laboratory phase, at the very least, let's make sure no bad things happen, or during this laboratory phase, at the very least, let's make sure that we don't block a pathway that might turn out to be meaningful, whether it turns out that federally qualified health centers or psychiatrists or methadone clinics or whatever end up playing a really crucial role in this.

So that's why I'll just say once more, I'm comfortable with the proposed REMS, roughly, as is. I would not be comfortable at this point adding more restrictions, registries, restricted access, or anything like that. I think that that would be

premature, and risk actually shutting off avenues by making the prescribing and receipt of PrEP so cumbersome that there won't be the uptake that we would need to really understand what we need to have in place. Thank you.

DR. ELLENBERG: I'll leave most of these questions to those who have clinical and practical expertise in this area, although I would say that it seems to me to be a good idea to have a baseline measure of bone mineral density. And how often that should be looked at would depend on the individual people, and maybe what that baseline level was.

With regard to metrics, one thought I had was that there are a number of existing observational databases of things that are kept by, for example, the NIH-sponsored programs, the Centers for AIDS Research, maybe even the multi-center AIDS cohorts even though they haven't entered anybody in 10 years, so they're not going to have the really young people.

But there are existing databases that

perhaps could be utilized to undoubtedly -- I know in our database, there are men who are seronegative, and undoubtedly some of people in these databases are going to start taking these medications. So perhaps that's a source without starting a new registry, and these data could be confidential. The people who keep them could provide data.

DR. BLOWER: Okay. Well, my comments relate to frequency of testing. It's essential to know that people are uninfected when they're first given PrEP. The frequency of testing, though, will depend very much on the incidence because that determines the probability, the likelihood, that you get infected.

So I don't think there should be a one-size-fits-all for frequency of testing. It should vary with risk groups and, potentially, geographic area.

You can do mathematical models of this, and actually, we published a model on this in PNAS in 2010. And we modeled PrEP and resistance in the San Francisco MSM community. What we found there

was anywhere between up to six months would minimize resistance in that population. So that's a fairly risky group.

I also think, and I'm sure people would agree, it's essential to develop intermittent regimens. Bob Grant had some interesting data on that, showing the efficacy with different number of doses a week, and there are some interesting studies in their macaques. That would definitely decrease the adherence problems, and also increase the cost-effectiveness.

Then finally, one thing I want to say about PrEP and resistance, we've all been concerned about increasing resistance. But it's actually possible for PrEP to decrease resistance. And again, we've modeled and published that. And how that works is if PrEP is effective enough and reduces incidence, there's fewer need for treatment, and most of the resistance will come out of treatment programs. So if you get to a certain coverage and efficacy level, then you reduce the actual resistance levels.

DR. NEWCOMER: Susan Newcomer. I'll also have to leave the ideas of testing incidence to the clinicians, although I like Dr. Blower's idea that it ought to be geographically relevant to the incident's prevalence in the community.

I also respect Dr. Feinberg's perspectives on the way to do positive education, and the comment that perhaps some kind of checklist and/or a contract between the provider and the person who is getting PrEP would be a very good idea; even if it only went into the files, it might be helpful in terms of making sure, or attempting to make sure, that adherence is okay.

That's it.

DR. CORBETT: Amanda Corbett. I only have two hopefully brief additional comments. One would be for the HIV testing at baseline, and then I agree with what folks have said so far.

Just a consideration for those that have a large volume of users, to consider HIV antibody testing and then antibody-negatives, doing pooled HIV RNA assessments, if you have a large volume

that you're trying to test.

Then secondly -- it may not be a terribly popular comment -- but just to add that you could use therapeutic drug monitoring of tenofovir in these patients as one additional tool, realizing that it's not widely used in the United States, but that is an option. And clearly it was utilized a lot in these clinical trials and likely will continue to do so in continuing trials also.

DR. GIORDANO: Tom Giordano. I have some comments I hope that are not duplicated.

First, in terms of testing, I feel very, very strongly that you need an antigen-based assay at at least initiation. These studies found, in admittedly very high-risk populations, .2, .3, .4 incidence of acute HIV infection. That is off the charts when it comes to trying to find acute HIV infection compared to most studies.

So you've got a super-high-risk population, and you need to do a combination antibody/antigen test. A fourth generation HIV test would get that done. That's what the CDC is trying to move to, so

if you've got that test, you're done. If you don't have that test, I think you have to do a viral load. If you can't do that for some reason, then I think you need to do -- you could do a qualitative HIV test or maybe do another HIV test pretty frequently.

In terms of the frequency of safety monitoring, I would favor bringing the patient back relatively quickly initially. There was quite a bit of -- it looked like side effects early on in the treatment. So I would say you bring them -- patients should be brought back in a couple weeks initially, just to manage side effects. I think that might promote better adherence. I'm not sure if that was done in these studies; I imagine it was.

But some early, more frequent monitoring for side effects and adverse effects with laboratory monitoring might be indicated, maybe monthly for the first couple months, and then you can spread it out once you figure out, A, is the patient actually going to stay on the medicine, and B, are they

having any side effects that would need to be addressed. So I think, ultimately, a three-month interval probably makes sense for repeat HIV testing.

As to the other safety parameters, I think we need to keep it simple so that it's not yet another barrier to using this medication. The DEXA scanning to me seems pretty far down the line unless you have some other risk factors for deceased bone mineral density.

There was an analysis that did not get presented but was in our materials that was done by FDA that showed the utility of alk phos in predicting -- elevated alk phos was predictive of people who were actually going to have bone mineral density problems on DEXA. I think maybe the FDA could pursue those analyses. That seemed like a nice, easy way to screen for problems.

Completely agree on the hepatitis B, the need for hepatitis B screening. And if someone is negative, then they should move to immunization since they're high risk for hepatitis B anyway.

In terms of the REMS, I feel very strongly that we want to minimize barriers here. This is a new tool for HIV prevention. We haven't had, really, a new tool in a while. Treatment as prevention isn't really new, folks. Maybe we're talking about it like it's new, but it's not that new. We've been trying to treat people for a long time, and the problem is not that we're deferring therapy; the problem is that people aren't getting diagnosed.

So treatment as prevention is not going to do a whole lot. This isn't a tool that we have that we can implement. And I would urge a few barriers. I think there's been some great ideas about what providers and patients can do together to improve outcomes, but I don't know which of those, if any, deserves to be a required element of a risk mitigation plan.

I do think I would require that there be community involvement in developing materials that get sent to providers as well as patients. I think there needs to be community involvement in that.

I would also strongly urge that there be something more than a statement that adherence is important. Everyone knows adherence is important. Knowledge is not enough to change adherence.

So it should include tools for adherence. It should include strategies to promote adherence. There's some excellent adherence researchers who are part of the two studies presented today. I'm sure they've got some of those tools.

Finally, I think there should be some information on drug-drug interactions because tenofovir does have some drug-drug interactions, and that should be part of the educational material. Thank you.

DR. KUHAR: Hi. I'm David Kuhar. I'll try to keep this as focused as I can here.

For frequency of HIV testing, I actually agree that baseline testing is incredibly important. I think we saw enough data that showed that missing infections and starting someone who is infected on suboptimal therapy leads to resistance.

So I think that for baseline testing, fourth

generation antigen/antibody testing is really a must, if that is available. You want to use a method that can detect HIV infection as early as possible, and there's good data for that testing platform. Otherwise, I agree that HIV RNA testing is what should be employed so we do not miss early infections.

As for how frequently HIV testing should be done after done initially, I also agree with sort of a tiered approach, doing things more frequently earlier on makes more sense. I think the testing every two to three months, at least initially, makes good sense and seems reasonable.

As for safety assessments that should be recommended, hepatitis B testing at baseline is absolutely necessary. Truvada is used for treating hepatitis B, not that uncommonly. And also, if you start someone on Truvada who has hepatitis B and you stop it, they will have a flare in their hepatitis B. So you can actually harm the patient. So hep B testing is a must, and it's also an opportunity for vaccinating those who are antibody-

negative and uninfected.

I think that renal testing -- I'm not going to begin to step on nephrologists' toes about which tests to send. But I think that, at least early on, it makes good sense. I like the idea of every three months, at least early on, and things could be spaced out later as also there's more data that we acquire.

I don't feel as strongly about DEXA, but I think at least initially, it does make sense to check, I think less frequently.

As for the REMS, for A, prescriber education program, including the appropriate target prescribers, I agree with comments already made about -- I liked the list of target prescribers, with the exception of emergency physicians. But I think there was agreement on that.

Then what metrics could be considered in the REMS assessment in addition to prescriber and user surveys. You know, I agree with comments that you don't want to make PrEP inaccessible by placing too many requirements. And it's hard to know how to

have just the right touch in something like this.

I would favor or lean towards a required training for prescribers only in that I suspect that a PrEP indication may recruit providers who are inexperienced in prescribing antiretrovirals, and that we may end up with new prescribers doing this. And I think that education in how to do this is very important. And I worry a little bit that receiving mailings might not be enough.

I very much liked -- actually, I don't mean to -- to backtrack a little, I like the idea of a patient/provider contract and checklist. I actually think that only serves as reminder to the patient what needs to be done, but it reminds the provider what they need to do as well.

But back to the REMS assessments. I also think that development of drug resistance is something that would be not only interesting but I think important to track, as this tells us, in a way, if we're on the right track or if we're seeing complications. It could be a little challenging in fleshing out, even if it's someone on PrEP, whether

the drug resistance was caused by PrEP or whether they had a drug-resistant virus transmitted to them.

Nonetheless, I think an idea of having a PrEP box on drug-resistance testing could help to flag that, and I would explore ways that we could look at it.

That's it.

DR. CHEEVER: And I've got about 25 minutes' worth of comments. Just kidding. I'll be brief here.

(Laughter.)

DR. CHEEVER: So the HIV testing, I agree that for the first test, either fourth generation -- that may not be available -- but something that'll look at antigen. I completely agree with the hepatitis B susceptibility, and to strongly encourage providers to vaccinate susceptible patients because my concern is, we know they're having high-risk sex in MSM. They're likely to seroconvert, and then we're going to get the flares, et cetera. So definitely need to do

thought.

For bone, I think that these studies have all been way too short to understand. We already see a significant dropoff after two years. What are we going to see later on? So maybe some sort of assessment of someone who's at increased risk for having low bone mineral density to begin with would get a DEXA, not everyone, because once again, I think that's too high a bar.

Renal function, I think, has been taken care of.

I just want to reiterate the issue around risk assessment. I can see a lot of doctors who know their patient is gay, and that's already too much information. And so they're just going to prescribe PrEP. So I think that we need to be talking to them about that it is a risk/benefit analysis and that people should be at high risk and not just gay because I think that it's just too much to manage.

In terms of the REMS, in terms of the targeted prescribers, in my mind in HIV prescribers

are PAs and NPs. I think I saw that on one of the lists but not the other lists. So definitely more than just physicians, particularly those who are going to see high-risk patients, so people that are in STD clinics and that sort of thing. That wasn't specifically mentioned on that list, but thinking about who actually takes care of high-risk patients, particularly mid-level providers.

And in that provider education, providers need to learn how to do sexual risk assessments because they don't know how to do it.

DR. PADIAN: A tiny little point just to build on the risk assessment. That was one of the reasons why I voted for all three because I think, as part of the training, physicians need to learn how to do that.

I have nothing new to add other than the importance of an active and representative surveillance, whether that's done as part of your REMS, or whether that's postmarketing, or both, because we can't ignore -- everyone's talking about the care and treatment cascade, that we can't

contribute to dropoff at step one.

But I'm more concerned with process than I am with content. I don't know what the process is because if I were you, I would be -- how can you assimilate what all of us are saying now and coming up with these lists? You know, we're all spent.

So what I'm wondering is, is there a process where -- and I know you guys are super-frustrated because it is challenging to come up with what could be done. But is there some process that you can engage in as a next step so that you can get help thinking that through, that you can vet it, and so that we also feel more comfortable?

Because I'm still not 100 percent sure whether we get to change them or not. But what is the process going forward? That's really -- and my only suggestion is, I hope that there is one.

DR. RUIZ: Well, I don't have too much to add because everyone has had excellent comments. I'll just say a couple things that I feel are terribly important.

I really, really, really strongly believe in

a baseline HIV test that includes fourth generation antibody/antigen, whatever we can do to try to detect acute infection if it has not been yet diagnosed. Hepatitis B, for obvious reasons, needs to be examined, tested for, vaccinations given, et cetera.

My comments on frequency of testing tend to be along the more conservative side. I would love to see -- I know this may not be possible -- I would love to see monthly testing and monthly visits, at the very least, for the reason at the very least so that the behavior of adherence can be helped along.

Establishing any sort of behavior change is difficult. The more assistance you give for people, support them in their behavior change, help them deal with roadblocks, barriers, obstacles, the better chance that they will adopt the behavior for the longer term.

So I think having monthly visits would be great. I don't know if that's possible; I will settle for every three months. But I think it's

important to have those regular visits early on as frequently as we can, without exhausting both patient and provider, so that we can get more data on real world usage, safety, resistance, et cetera, for a variety of populations that will be needing this drug, that will be using this drug, et cetera.

I will leave the comments on safety assessments to those who have spoken before me. I think there have been a lot of really great suggestions made, so I will second those.

I will also second the comments that have already been made with regard to the REMS. I think they need a lot more teeth. I think they can be much more proactive, almost aggressive, because I think we have a tremendous opportunity here to get data that we desperately need about real world usage.

Again, we are never going to be able to extrapolate, truly extrapolate, what's going to happen in the real world from clinical trials that have been done so carefully, so precisely, and even then things happened in these trials that we cannot

control.

In order for us to get real world data, we actually have to collect it, and that involves surveillance. That involves much, much more data collection than what is being proposed in both the FDA REMS and in the sponsor's REMS.

I think we could do better. I think we could do more. We could do more coordinated work here round that. And certainly some of these opportunities for some of this data collection and some of this effort can be done through postmarketing commitment surveys. I really think that can be -- we have a tremendous opportunity.

The one thing I think we really -- the opportunity we really have here is that we've been talking and we've been hearing from our community panelists who spoke earlier about how this is never going to work in the real world. In the real world, this doesn't happen. But the thing is, in the real world, our standard of care is not the same as the standard of care that's provided in these clinical trials, where adherence is optimized

because so many things are there to optimize the patient experience, and to bring the person back in, and to help that person through all of the roadblocks and barriers.

So why not take this opportunity to elevate the standard of care in the real world to what we're seeing in a clinical trial? Then we might see better adherence. We might get better safety profiles. We might get to see what that would look like. And if we collect those data early enough, we can correct things that have gone wrong early enough so that they don't progress to the point where they're very detrimental.

The only phrase that comes to mind is, "With great privilege comes great responsibility." We have a privilege of being able to talk about a new prevention strategy and a privilege of possibly making it available to people who really, really need it. And I think we'd be doing ourselves and them an injustice if we don't think about the best way to optimize that access for them, but also not shoot ourselves in the foot by pushing things out

too quickly.

DR. ROBINSON: Well, all the good ideas have been taken, almost.

(Laughter.)

DR. ROBINSON: But just to wrap up the comments on these questions, my recommendations would be to facilitate the baseline testing, that the agency consider strongly worded, strongly placed not recommendations but requirement in the label. This will obviously drive guidelines, and both of these mechanisms will be very instructive and drivers to the practicing physician.

The other thing that I think will be very helpful, and I'm confident that the sponsor is good at this sort of thing, is putting together not just a bland educational program but a scientifically driven, evidence-based, guidelines-based, in-person face-to-face kinds of educational programs. And these the things that some sponsors ought to be able to embrace.

Then finally, to assess how things are going, you need more than just a virtual survey.

You need something more than SurveyMonkey online, some real shoe leather epidemiology in the setting of practice, or in the setting of a real demonstration study, not a clinical trial study but a real demonstration study.

So those are the recommendations I have to make.

DR. FEINBERG: Great. Thank you all for all those very creative thoughts.

We have two more questions to address, but --

DR. COX: Dr. Feinberg?

DR. FEINBERG: What do you want me to do?

DR. COX: I think we're going to have to wrap up at this point.

DR. FEINBERG: All right. Then I'm not going to --

DR. COX: Yes. Let me first just express my tremendous gratitude to the committee. This has been a marathon day, and people have really hung in there well. And I really do appreciate all the comments that folks have made; it's really been

tremendous to hear all the thoughtful comments that we've heard over the course of the day.

I know Dr. Birnkrant wants to make a final statement, too. And then perhaps if we can turn it back to you at that point, Dr. Feinberg, is that fair? Okay.

DR. BIRNKRANT: Well, this is truly a landmark meeting on many levels, on landmark data. So on behalf of the FDA, I want to thank the committee members for their advice on Truvada for a PrEP indication in combination with other prevention methods in certain uninfected high-risk adults to reduce the risk of sexually acquired HIV.

We appreciate the time you have taken to participate in this productive discussion and your recommendations on how the agency should proceed in regards to this application.

We also owe our thanks to the guest presenters and the applicant for participating in this meeting. We would also like to thank the open public hearing speakers for sharing their opinions on using Truvada as pre-exposure prophylaxis. Your

comments were valuable to the review process.

I would like to remind everyone that the docket for this meeting is still open, and I encourage all interested parties or people to submit comments before the docket closes on May 17th.

We understand there is great interest in this important public health issue, as there should be. It's back on the front pages. It has been made clear from our discussion today that the HIV epidemic in the United States continues unabated, and more must be done prevent new infections from occurring. We will continue our assessment of this application, taking the committee's recommendations and all public comments into consideration.

I would also like to thank our dedicated and diligent review team at the FDA; they've done an excellent job.

(Applause.)

DR. BIRNKRANT: And I would like to thank our very helpful advisors and consultant staff, who worked tirelessly with us to put this meeting

together. And I also want to thank Dr. Feinberg. Thank you all very much.

(Applause.)

DR. FEINBERG: So in closing, I just am glad you mentioned landmark because I think this meeting actually went longer than March 1, 1996, which was indinavir and ritonavir, and that was a landmark moment in the management of HIV disease.

Really, it was heroic, and thank everybody for your attention and energy. We've been at this for 12 hours.

(Laughter.)

Adjournment

DR. FEINBERG: On that note, we will adjourn the meeting.

(Whereupon, at 8:27 p.m., the committee was adjourned.)