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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING  
(AMDAC)

Wednesday, August 7, 2019

8:30 a.m. to 4:54 p.m.

FDA White Oak Campus  
White Oak Conference Center  
Building 31, The Great Room  
10903 New Hampshire Avenue  
Silver Spring, Maryland

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

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4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

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9 **(Voting)**

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11 *(Chairperson)*

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13 Division of Infectious Diseases

14 Brigham and Women's Hospital

15 Director, Infectious Disease Service

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17    *(Consumer Representative)*

18    Chief Executive Officer

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20    Mableton, Georgia

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3     Branch Chief

4     Research Regulatory Oversight Office

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6     (Personnel and Readiness)

7     Defense Health Headquarters

8     Falls Church, Virginia

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11    **Laura W. Cheever, MD, ScM**

12    Associate Administrator, HIV/AIDS Bureau

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**Matthew Bidwell Goetz, MD**

Chief, Infectious Diseases

VA Greater Los Angeles Healthcare System

Professor of Clinical Medicine

David Geffen School of Medicine at UCLA

Los Angeles, California

**Patricia Lupole** *(via phone)*

*(Patient Representative)*

Norfolk, Virginia

**Sarah W. Read, MD, MHS**

Deputy Director, Division of AIDS

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2 Biomedical Interventions Implementation Activity

3 Lead

4 Epidemiology Branch, Division of HIV/AIDS

5 Prevention

6 National Center for HIV, Viral Hepatitis, STD, and

7 Tuberculosis Prevention

8 Centers for Disease Control and Prevention

9 Atlanta, Georgia

10

11 **ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE**

12 **(Non-Voting)**

13 **Walid M. Awni, PhD**

14 *(Acting Industry Representative)*

15 Awni BioPharmaceutical Consulting, LLC

16 Riverwoods, Illinois

17

18 **FDA PARTICIPANTS (Non-Voting)**

19 **John Farley, MD, MPH**

20 Deputy Director

21 Office of Antimicrobial Products (OAP)

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Office of New Drugs (OND), CDER, FDA

1     **Debra Birnkrant, MD**

2     Director

3     Division of Antiviral Products (DAVP)

4     OAP, OND, CDER, FDA

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6     **Jeffrey Murray, MD, MPH**

7     Deputy Director

8     DAVP, OAP, OND, CDER, FDA

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10    **Wendy Carter, DO**

11    Medical Officer Team Leader

12    DAVP, OAP, OND, CDER, FDA

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14    **Peter Miele, MD**

15    Medical Officer

16    DAVP, OAP, OND, CDER, FDA

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18    **Jenny H. Zheng, PhD**

19    Clinical Pharmacology Reviewer

20    Division of Clinical Pharmacology IV

21    Office of Clinical Pharmacology

22    Office of Translational Sciences, CDER, FDA

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P R O C E E D I N G S

(8:30 a.m.)

**Call to Order**

**Introduction of Committee**

1 DR. BADEN: It's 8:30. Good morning. I  
2 would first like to remind everyone to please  
3 silence your cell phones, smartphones, and any  
4 other devices if you have not already done so. I  
5 would also like to identify the FDA press contacts,  
6 Alison Hunt and Charles Kohler. If you're present,  
7 please stand. They're in the back. If there are  
8 questions for the press, please address them to  
9 Alison and Charlie.

10 My name is Lindsey Baden. I will be  
11 chairing today's meeting. I will now call the  
12 Antimicrobial Drugs Advisory Committee to order.  
13 We'll start by going around the table and  
14 introducing ourselves. We'll start with the FDA to  
15 my left and go around the table.

16 DR. FARLEY: Good morning. John Farley,  
17 deputy director of the Office of Antimicrobial  
18 Products, CDER, FDA.

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

3 DR. MURRAY: Jeff Murray, deputy, Division  
4 of Antiviral Products, CDER, FDA.

5 DR. CARTER: Wendy Carter, clinical team  
6 leader, Division of Antiviral Products, CDER, FDA.

7 DR. MIELE: Pete Miele, medical officer,  
8 Division of Antiviral Products, CDER, FDA.

9 DR. ZHENG: Jenny Zheng, clinical  
10 pharmacology reviewer for antiviral products, CDER,  
11 FDA.

12 DR. CHEEVER: Hi. I'm Laura Cheever from  
13 the HIV/AIDS Bureau at the Health Resources and  
14 Services Administration.

15 DR. SWAMINATHAN: I'm Shankar Swaminathan,  
16 infectious diseases division chief at the  
17 University of Utah.

18 DR. SIBERRY: George Siberry, Office of  
19 HIV/AIDS, Global Health Bureau, USAID.

20 DR. GRIPSHOVER: Barbara Gripshover from  
21 University Hospitals Cleveland, Case Western  
22 Reserve University, adult infectious disease.

1 DR. GREEN: Michael Green, University of  
2 Pittsburgh School of Medicine, Children's Hospital  
3 Pittsburgh, pediatric infectious diseases.

4 DR. WEINA: Peter Weina, adult infectious  
5 diseases, Research Regulatory Oversight Office,  
6 Defense Health Headquarters.

7 DR. HOTAKI: Lauren Hotaki, designated  
8 federal officer.

9 DR. BADEN: Lindsey Baden, adult infectious  
10 diseases, Brigham and Women's Hospital, Dana Farber  
11 Cancer Institute, Harvard Medical School, Boston  
12 Mass.

13 DR. OFOTOKUN: Igho Ofotokun, adult  
14 infectious diseases, Emory University, Atlanta,  
15 Georgia.

16 DR. BURGESS: Tim Burgess, adult infectious  
17 diseases. I'm director of DoD's Infectious Disease  
18 Clinical Research Program at Uniform Services  
19 University.

20 DR. LE: Jennifer Le, professor of pharmacy  
21 at UC San Diego, pediatric infectious diseases.

22 DR. WALKER: Good morning. Dr. Roblena

1 Walker, EMAGAHA, Inc., Atlanta, Georgia, consumer  
2 representative.

3 DR. GIORDANO: Tom Giordano, adult  
4 infectious disease, Baylor College of Medicine and  
5 the Michael E. DeBakey VA Medical Center, Houston,  
6 Texas.

7 DR. DASKALAKIS: Demetre Daskalakis, adult  
8 infectious diseases, and also deputy commissioner  
9 for disease control at the New York City Department  
10 of Health and Mental Hygiene.

11 DR. READ: Sarah Read, deputy director of  
12 the Division of AIDS at the National Institute of  
13 Allergy and Infectious Diseases.

14 DR. SMITH: Hi. Dawn Smith, medical  
15 epidemiologist, Centers for Disease Control and  
16 Prevention.

17 DR. GOETZ: Matthew Goetz, VA Greater Los  
18 Angeles Healthcare System, David Geffen School of  
19 Medicine, adult infectious diseases.

20 DR. AWNI: Walid Awni, retired. I retired  
21 from AbbVie last year as vice president of clinical  
22 pharmacology and pharmacometrics. I'm the acting

1 industry representative.

2 DR. BADEN: Thank you. Dr. Dodd?

3 DR. DODD: Dr. Dodd, biostatistician at  
4 National Institute of Allergy and Infectious  
5 Diseases.

6 DR. BADEN: I think we may have someone on  
7 the phone. Ms. Lupole?

8 MS. LUPOLE: Yes, sir. Good morning  
9 [inaudible -feedback].

10 DR. BADEN: You have a bit of feedback.

11 MS. LUPOLE: I'm sorry. Can you hear me  
12 now?

13 DR. BADEN: Yes, we can.

14 MS. LUPOLE: Patricia Lupole, patient  
15 representative.

16 DR. BADEN: Thank you.

17 For topics such as those being discussed at  
18 today's meeting, there are often a variety of  
19 opinions, some of which are quite strongly held.  
20 Our goal is that today's meeting will be a fair and  
21 open forum for discussion of these issues and that  
22 individuals can express their views without

1 interruption. Thus, as a gentle reminder,  
2 individuals will be allowed to speak into the  
3 record only if recognized by the chairperson. We  
4 look forward to a productive meeting.

5 In the spirit of the Federal Advisory  
6 Committee Act and the Government in the Sunshine  
7 Act, we ask that the advisory committee members  
8 take care that their conversations about the topic  
9 at hand take place in the open forum of the  
10 meeting.

11 We are aware that members of the media are  
12 anxious to speak with the FDA about these  
13 proceedings. However, FDA will refrain from  
14 discussing the details of this meeting with the  
15 media until its conclusion. Also, the committee is  
16 reminded to please refrain from discussing the  
17 meeting topic during breaks or lunch. Thank you.

18 I thank everyone for making the time to be  
19 here to participate in this discussion. We know  
20 how busy everyone is.

21 I will ask Dr. Lauren Hotaki to read the  
22 Conflict of Interest Statement for the meeting.

1                                   **Conflict of Interest Statement**

2                   DR. HOTAKI:   The Food and Drug  
3           Administration is convening today's meeting of the  
4           Antimicrobial Drugs Advisory Committee under the  
5           authority of the Federal Advisory Committee Act of  
6           1972.   With the exception of the industry  
7           representative, all members and temporary voting  
8           members of the committee are special government  
9           employees or regular federal employees from other  
10          agencies and are subject to federal conflict of  
11          interest laws and regulations.

12                   The following information on the status of  
13          this committee's compliance with federal ethics and  
14          conflict of interest laws, covered by but not  
15          limited to those found at 18 U.S.C. Section 208, is  
16          being provided to participants in today's meeting  
17          and to the public.

18                   FDA has determined that members and  
19          temporary voting members of this committee are in  
20          compliance with federal ethics and conflict of  
21          interest laws.   Under 18 U.S.C. Section 208,  
22          Congress has authorized the FDA to grant waivers to

1 special government employees and regular federal  
2 employees who have potential financial conflicts  
3 when it is determined that the agency's need for a  
4 special government employee's services outweighs  
5 his or her potential financial conflict of  
6 interest, or when the interest of a regular federal  
7 employee is not so substantial as to be deemed  
8 likely to affect the integrity of the services  
9 which the government may expect from the employee.

10 Related to the discussion of today's  
11 meeting, members and temporary voting members of  
12 this committee have been screened for potential  
13 financial conflicts of interest of their own as  
14 well as those imputed to them, including those of  
15 their spouses or minor children, and, for purposes  
16 of 18 U.S.C. Section USC Section 208, their  
17 employers. These interests may include  
18 investments; consulting; expert witness testimony;  
19 contracts, grants, CRADAs; teaching, speaking,  
20 writing; patents and royalties; and primary  
21 employment.

22 Today's agenda involves discussion of

1 supplemental new drug application 208215,  
2 supplement 12, DESCOVY, emtricitabine  
3 200 milligrams and tenofovir alafenamide  
4 25 milligrams submitted by Gilead Sciences, Inc.,  
5 proposed for pre-exposure prophylaxis to reduce the  
6 risk of sexually acquired HIV-1 infection among  
7 individuals who are HIV negative and at risk for  
8 HIV. This is a particular matters meeting during  
9 which specific matters related to Gilead's sNDA  
10 will be discussed.

11 Based on the agenda for today's meeting and  
12 all financial interests reported by the committee  
13 members and temporary voting members, conflict of  
14 interest waivers have been issued in accordance  
15 with 18 U.S.C. Section 208(b)(3) to Dr. Lindsey  
16 Baden and Dr. Barbara Gripshover.

17 Dr. Baden's waiver addresses his employer's  
18 current research contract for related study by a  
19 competing firm for which his employer receives  
20 between \$0 and \$50,000 annually. Dr. Baden's waiver  
21 also addresses his employer's current research  
22 contract for related studies through the HIV

1 Vaccine Trials Network sponsored by the National  
2 Institute of Allergy and Infectious Diseases of the  
3 National Institutes of Health and a competing firm,  
4 for which his employer receives \$1.5 to \$2.5  
5 million annually.

6 Dr. Gripshover's waiver addresses her  
7 employer's current research contracts for four  
8 related studies involving competing/affected  
9 products for which her employer receives between  
10 \$50,001 to \$100,000 annually for two studies, and  
11 between \$300,000 to \$400,000 annually, and to \$0 to  
12 \$50,000 annually for the other two studies.

13 The waivers allow these individuals to  
14 participate fully in today's deliberations. FDA's  
15 reasons for issuing the waivers are described in  
16 the waiver documents, which are posted at the FDA's  
17 website. Copies of the waivers may also be  
18 obtained by submitting a written request to the  
19 agency's Freedom of Information Division,  
20 5630 Fishers Lane, Room 1035, Rockville, Maryland,  
21 20857, or requests may be sent via fax to 301-827-  
22 9267.

1           To ensure transparency, we encourage all  
2 standing committee members and temporary voting  
3 members to disclose any public statements that they  
4 have made concerning the product at issue. With  
5 respect to FDA's invited industry representative,  
6 we would like to disclose the Dr. Walid Awni is  
7 participating in this meeting as a nonvoting  
8 industry representative, acting on behalf of  
9 regulated industry. Dr. Awni's role at this meeting  
10 is to represent industry in general and not any  
11 particular company. Dr. Awni is an independent  
12 pharmaceutical consultant.

13           We'd like to remind members and temporary  
14 voting members that if the discussions involved any  
15 other products or firms not already on the agenda  
16 for which an FDA participant has a personal or  
17 imputed financial interest, the participants need  
18 to exclude themselves from such involvement, and  
19 their exclusion will be noted for the record. FDA  
20 encourages all other participants to advise the  
21 committee of any financial relationships that they  
22 may have with the firm at issue. Thank you.

1 DR. BADEN: Thank you.

2 We will proceed with the FDA opening remarks  
3 from Dr. Murray.

4 **FDA Opening Remarks - Jeffrey Murray**

5 DR. MURRAY: Good morning. The Division of  
6 Antiviral Products extends its warm welcome to the  
7 committee and to the audience to discuss a new  
8 supplemental application for Descovy, for the  
9 prevention of sexually-acquired HIV infection, and  
10 we're happy to be talking about expanding the HIV  
11 prevention armamentarium today.

12 Some of you on the panel, and perhaps in the  
13 audience, may have been here in 2012, in this very  
14 room -- I know I was -- when the advisory committee  
15 voted on whether Truvada should be approved for  
16 PrEP. As you recall, the committee voted yes, and  
17 Truvada became the first U.S. approved product for  
18 PrEP, and really the first product for HIV PrEP for  
19 sexually-acquired HIV infection anywhere in the  
20 world. Fast forward to seven years, and that  
21 brings us to today's topics.

22 There are similarities and differences

1 between these two products. Both our fixed-dose  
2 combinations that contain emtricitabine. Both  
3 contain a prodrug of tenofovir with the same active  
4 metabolite. Both are approved for HIV treatment,  
5 both of the products. Tenofovir components are  
6 also approved as single agents for the treatment of  
7 chronic hepatitis B.

8           However, there are also differences,  
9 specifically as they relate to the bioavailability  
10 of tenofovir as delivered by these two different  
11 prodrugs in these fixed-dose combination. Descovy  
12 delivers lower levels of plasma tenofovir in tissue  
13 and organs and higher levels of intracellular  
14 tenofovir diphosphate of active metabolite.

15           As I said, there are also differences in  
16 tissue and organ distribution. This results in  
17 somewhat a different safety profile, but did not  
18 result in efficacy differences for HIV treatment.  
19 The other differences, Truvada is already approved  
20 for prevention and Descovy is not, and that's a  
21 topic for today.

22           To support the prevention indication of

1 Truvada, I remind you the applicant submitted two  
2 clinical trials, a clinical trial in MSM  
3 transgender women, iPrEx, and a trial in discordant  
4 heterosexual couples, Partners PrEP, which allowed  
5 for a broad indication among at-risk populations.  
6 Today we're dealing with one clinical trial.

7           What are some of the regulatory  
8 considerations about the basis of supporting an  
9 approval? Really, the number of clinical trials  
10 needed to support an approval depends on the  
11 regulatory situation.

12           For a new molecule entering the market,  
13 generally two or more drugs are expected -- or two  
14 or more trials are expected. However, for a new  
15 and related indication for a previously approved  
16 drug, often only one trial is needed to support  
17 approval.

18           Likewise, if there's a new dosing schedule,  
19 say twice daily to once daily, and you can't make a  
20 pharmacokinetic link, that's also been supported by  
21 one trial, or for a new population where PK is  
22 different, usually we rely on one clinical trial.

1           For Descovy, FDA's initial drug development  
2           advice was that clinical trials should be conducted  
3           in the relevant population, and that a PK link  
4           alone would not be possible. So for this  
5           application, as I said, we have one trial in MSM  
6           and transgender women but none in cisgender women  
7           at risk.

8           The primary issue for today and what you'll  
9           be asked in the question is given the uncertainty  
10          around the protective correlate, can extrapolation  
11          be used to further expand the indicated population?

12          With that being said, this application is a  
13          special case in the development of drugs for HIV  
14          prevention, and with that, I have the following  
15          caveat that the approach for Descovy may not apply  
16          to future new molecular entities because in this  
17          case, a prodrug, tenofovir for PrEP, has already  
18          been approved, and there is a possibility that data  
19          within and external to the Descovy program can be  
20          leveraged. So we ask the committee today for their  
21          advice on how this data can be best leveraged.  
22          Thank you.

1 DR. BADEN: Thank you. We'll now move on to  
2 the applicant presentations.

3 Both the FDA and the public believe in a  
4 transparent process for information gathering and  
5 decision making. To ensure such transparency at  
6 the advisory committee meeting, FDA believes that  
7 it is important to understand the context of an  
8 individual's presentation.

9 For this reason, FDA encourages all  
10 participants, including the applicant's  
11 non-employee presenters, to advise the committee of  
12 any financial relationships they may have with the  
13 applicants, such as consulting fees, travel  
14 expenses, honoraria, an interest in a sponsor,  
15 including equity interests and those based upon the  
16 outcome of the meeting.

17 Likewise, FDA encourages you at the  
18 beginning of your presentation to advise the  
19 committee if you do not have any such financial  
20 relationships. If you choose not to address this  
21 issue of financial relationships at the beginning  
22 of your presentation, it will not preclude you from

1 speaking.

2 We'll now proceed with Gilead's  
3 presentations. Dr. Brainard?

4 **Applicant Presentation - Diana Brainard**

5 DR. BRAINARD: Good morning. Ending the HIV  
6 epidemic requires not just highly effective  
7 treatments for people who have already been  
8 infected, but additional options for preventing new  
9 infections.

10 My name is Diana Brainard, and I lead the  
11 HIV and emerging viruses group at Gilead Sciences.  
12 I am an infectious diseases physician and have  
13 worked as a clinician and scientist in both the  
14 U.S. and Africa to care for people living with HIV  
15 and tackle the epidemic. It is a pleasure and  
16 honor to be here today to work with this committee  
17 to bring forward another HIV prevention option that  
18 will help us achieve our shared goal of HIV  
19 elimination.

20 Seven years ago, as Dr. Murray mentioned,  
21 Truvada was approved to prevent sexually-acquired  
22 HIV infection and remains today the only approved

1 therapy for HIV pre-exposure prophylaxis or PrEP.  
2 Truvada is the fixed-dose combination of 2 HIV  
3 reverse transcriptase inhibitors, emtricitabine and  
4 tenofovir disoproxil fumarate. Truvada is approved  
5 as part of a complete regimen for the treatment of  
6 HIV in adults and adolescents, as well as for PrEP.

7 Tenofovir disoproxil fumarate is also  
8 approved as a single agent for the treatment of  
9 chronic hepatitis B. Descovy is the fixed-dose  
10 combination tablet of emtricitabine and tenofovir  
11 alafenamide. It is approved for HIV treatment, and  
12 tenofovir alafenamide is approved as a single agent  
13 for treatment of chronic hepatitis B. Descovy is  
14 not approved for PrEP.

15 We are proposing an indication for Descovy  
16 for PrEP in adults and adolescents based on the  
17 data we are discussing today. Tenofovir disoproxil  
18 fumarate and tenofovir alafenamide are both  
19 prodrugs of tenofovir, but they have markedly  
20 different metabolism. Tenofovir alafenamide, or  
21 TAF, is dosed at one 12th that of tenofovir  
22 disoproxil fumarate, or TDF, because of the

1 difference in half-life.

2 TDF is rapidly converted to tenofovir, or  
3 TFV, resulting in high plasma tenofovir levels  
4 which have direct and indirect adverse effects on  
5 kidney and bone. The half-life of TAF is 75 times  
6 longer than that of TDF, which results in  
7 90 percent lower plasma tenofovir levels.  
8 Descovy's lower levels of circulating tenofovir  
9 translate to fewer clinically relevant adverse  
10 renal and bone effects.

11 The longer half-life of TAF also allows it  
12 more time to enter peripheral blood mononuclear  
13 cells. Intracellularly, TAF is metabolized to the  
14 active metabolite, tenofovir diphosphate, or  
15 TFV-DP, where it achieves 4 to 7-fold higher levels  
16 of tenofovir diphosphate than those achieved by  
17 TDF.

18 For both TAF and TDF, tenofovir diphosphate  
19 within PBMCs and specifically CD-4 positive  
20 T cells, is responsible for the inhibition of HIV  
21 replication, which leads to protection against HIV  
22 infection in the setting PrEP, as well as viral

1 suppression in the case of HIV treatments.

2 Tenofovir diphosphate is an adenosine analog  
3 that inhibits the enzyme HIV reverse transcriptase,  
4 which transcribes HIV RNA into proviral DNA. This  
5 mechanism of action is the same for both the  
6 prevention of HIV acquisition as well as for  
7 suppression of viremia in the setting of treatment,  
8 and the level of intracellular tenofovir  
9 diphosphate correlates with antiviral activity.

10 Pharmacokinetic differences between TAF and  
11 TDF result not only in higher levels of tenofovir  
12 diphosphate with TAF versus TDF, but also a faster  
13 rise of tenofovir diphosphate levels within PBMCs,  
14 including the target cells for HIV replication,  
15 CD-4 positive T cells. After a single dose,  
16 Descovy achieves intracellular tenofovir  
17 diphosphate levels above 40 femtomoles per million  
18 cells within 2 hours.

19 This threshold is relevant for PrEP based on  
20 its correlation using Truvada clinical data from a  
21 trial in men who have sex with men, with a  
22 90 percent reduction in risk of HIV acquisition as

1 compared to placebo.

2 In contrast, Truvada takes approximately  
3 3 days for the mean level to reach this EC<sub>90</sub>, and  
4 steady state levels remain lower than those for  
5 Descovy. Once steady state is achieved with either  
6 Descovy or Truvada, if drug is stopped, tenofovir  
7 diphosphate levels start to decline at a similar  
8 rate. However, since levels are so much higher  
9 with Descovy as compared to Truvada, they remain  
10 above this EC<sub>90</sub> for 16 days with Descovy compared  
11 with 10 days for Truvada.

12 These pharmacokinetic advantages of Descovy  
13 suggested to us that Descovy could be highly  
14 effective for PrEP, and the safety advantages  
15 observed in people living with HIV taking Descovy  
16 could also be realized among those at risk for HIV  
17 infection.

18 In 2015, when the DISCOVER study design was  
19 coming together, there was uncertainty around  
20 whether drug levels in the genital tract or  
21 peripheral blood mononuclear cells best correlated  
22 with protection against HIV. The higher levels of

1 Tenofovir diphosphate in PBMCs with Descovy could  
2 potentially confer an efficacy advantage and offer  
3 a more forgiving regimen for PrEP, provided these  
4 levels correlated with protection. However, if  
5 genital tract tissue levels drive efficacy, Descovy  
6 could be less effective for prevention.

7 Data from healthy volunteers show that  
8 rectal tissue levels are 10-fold lower following  
9 Descovy administration compared to Truvada. Our  
10 hypothesis was that prevention efficacy for oral  
11 drugs would be best measured by peripheral blood  
12 mononuclear cell drug levels rather than tissue  
13 homogenate levels, and that, therefore, Descovy  
14 would be at least as efficacious as Truvada in  
15 spite of this difference in rectal tissue levels.

16 This hypothesis was based on advances in the  
17 understanding of mucosal transmission of HIV. HIV  
18 must first breach the epithelium to reach the  
19 subepithelium, and it is generally believed that a  
20 single cell first becomes infected and initiates  
21 subsequent events.

22 Chemokines, primarily secreted by

1 plasmacytoid dendritic cells, attract PBMCs.  
2 Specifically, CD-4 positive and CD-8 positive  
3 T cells from the pool of PBMCs traffic from the  
4 circulation to the tissue. This then results in a  
5 small founder population of initially infected CD-4  
6 T cells located in the subepithelium.

7           The recruitment of target cells for HIV, the  
8 CD-4 T cells, from the periphery is critical in  
9 order for systemic infection to occur.

10 Dissemination of these recruited and now infected  
11 CD-4 positive T cells occurs as they enter the  
12 lymphatic system to travel to regional lymph nodes  
13 and spread throughout the body.

14           Protection against systemic HIV infection  
15 can occur via both topical and systemic modalities.  
16 Topical antiretrovirals, such as investigational  
17 tenofovir gel, allow for the diffusion of drug into  
18 tissues within the genital tract. Efficacy depends  
19 on reaching therapeutic levels intracellularly  
20 within the local CD-4 positive T cells. These  
21 methods have generally proven less effective than  
22 PrEP delivered systemically.

1 Truvada and Descovy distribute widely  
2 throughout the body and can offer a greater degree  
3 of protection. They can both reach the genital  
4 tissues through the blood supply, where they can  
5 then access resident lymphocytes.

6 Importantly as well, PBMCs that contain the  
7 active metabolite of both Truvada and Descovy,  
8 tenofovir diphosphate also can reach the genital  
9 tract and can be among the cells recruited to the  
10 site of initial infection, as well as into the  
11 regional draining lymph nodes so as to prevent  
12 systemic infection.

13 While there has been no clear evidence of a  
14 correlation of preventive efficacy of Truvada for  
15 PrEP with tissue levels, efficacy strongly  
16 correlates with drug levels of tenofovir  
17 diphosphate within PBMCs.

18 A subset of participants in the IPREX study,  
19 in men who have sex with men of Truvada versus  
20 placebo, had tenofovir diphosphate levels assessed  
21 in PBMCs. Because of the wide range of adherence  
22 and that trial and the placebo arm to which a

1 direct comparison could be made, it was possible to  
2 construct a relationship between PBMC tenofovir  
3 diphosphate levels and risk production with respect  
4 to HIV incidence.

5 It was with these data that Dr. Anderson  
6 established the correlate of protection for  
7 90 percent risk reduction for tenofovir diphosphate  
8 levels at 40 femtomoles per million PBMCs and  
9 showed that there's a range of protection above and  
10 below that level. These data are now well  
11 recognized and have been cited in the most recent  
12 CDC PrEP guidance issued on July 18th of this year.

13 When the DISCOVER study was being designed,  
14 the scientific and clinical understanding of HIV  
15 prevention was less mature. At that time, Truvada  
16 for PrEP was only approved in adults. Descovy was  
17 under review by the FDA for the treatment of HIV.  
18 We knew that rectal tissue levels with Descovy were  
19 10-fold lower than those achieved with Truvada.

20 If the primary driver for prevention  
21 efficacy, with orally administered tenofovir  
22 prodrugs is local tissue drug levels, then Truvada

1 should be better than Descovy at preventing HIV  
2 infection. However, if obtaining high levels in  
3 PBMCs is what's important, then Descovy should be  
4 at least as effective as Truvada.

5 This question was addressed in the phase 3  
6 DISCOVER trial. The DISCOVER trial, an  
7 international phase 3 study, was conducted to  
8 assess the safety and efficacy of Descovy for HIV  
9 prevention. This was a double-blind, active  
10 comparator, noninferiority trial, comparing Descovy  
11 to the standard of care for prevention, Truvada.

12 The study enrolled over 5,000 cis men and  
13 transgender women who have sex with men. The trial  
14 was designed and conducted in close collaboration  
15 with FDA and the community. Importantly, the study  
16 met its primary endpoint, demonstrating  
17 noninferiority of Descovy to Truvada for the  
18 prevention of HIV infection.

19 Among individuals randomized to Descovy, 7  
20 acquired HIV infection for an incidence rate of  
21 0.16 per 100 person-years. In the Truvada group,  
22 there were 15 infections resulting in an incidence

1 rate of 0.34 per 100 person-years. The incident  
2 rate ratio, the prespecified method for determining  
3 noninferiority, was 0.47 with an upper bound of the  
4 confidence interval less than the prespecified  
5 margin of 1.62.

6 Additionally, the prespecified  
7 alpha-controlled secondary safety endpoints were  
8 met, demonstrating superiority of Descovy to  
9 Truvada with respect to markers of bone and renal  
10 toxicity. Collectively, these data demonstrate  
11 that Descovy is highly effective at preventing HIV  
12 acquisition and demonstrates safety benefits over  
13 Truvada.

14 What we know now is that both Truvada and  
15 Descovy are highly effective for PrEP if taken.  
16 Adherence is the key determinant of efficacy. A  
17 correlate of protection has been established for  
18 tenofovir diphosphate levels in PBMCs. The  
19 DISCOVER trial confirms that 10-fold lower rectal  
20 levels of tenofovir diphosphate with Descovy versus  
21 Truvada are not relevant for HIV protection, and  
22 that the 7-fold higher tenofovir diphosphate levels

1 with Descovy versus Truvada might confer a  
2 potential efficacy advantage for Descovy.

3           These results support the conclusion that  
4 PBMC drug levels drive the efficacy of orally  
5 administered tenofovir prodrugs. This finding is  
6 an important consideration for the extrapolation of  
7 the DISCOVER results from cis men and transgender  
8 women to cis women.

9           To date, clinical trials in women have had  
10 heterogeneous efficacy results reflecting highly  
11 variable adherence. Data from clinical trials  
12 demonstrate that when controlling for adherence,  
13 Truvada is equally efficacious in women and men.  
14 There is a biologic rationale for this finding.

15           The biology of HIV as well as the  
16 intracellular antiviral activity of tenofovir  
17 diphosphate are independent of gender. HIV  
18 replicates within CD-4 positive lymphocytes, which  
19 must be recruited to the site of initial infection  
20 in order to successfully lead to systemic  
21 transmission. Adequate drug levels within these  
22 recruited cells are necessary and sufficient to

1 mediate protection against HIV infection.

2 Multiple lines of evidence support bridging  
3 the efficacy results for Descovy for PrEP from the  
4 men and transgender women in DISCOVER to ciswomen.  
5 In the setting of HIV treatment, the efficacy and  
6 safety of Descovy-based therapy have been well  
7 established in over 2000 women and are comparable  
8 to results in men.

9 Descovy and Truvada both inhibit HIV  
10 replication in CD-4 T cells through the same active  
11 metabolite, tenofovir diphosphate. Extensive  
12 pharmacology assessments have demonstrated that the  
13 levels of tenofovir diphosphate are similar  
14 irrespective of HIV status or gender. Taken  
15 together, these data support the use of Descovy for  
16 HIV prevention in women.

17 There is similar support for the  
18 extrapolation to adolescence. Descovy and the  
19 three other Descovy-containing single-tablet  
20 regimens are all indicated for HIV treatment in  
21 adolescence based on the safety and efficacy  
22 established in this group. HIV behaves similarly

1 independent of age, and therefore the extension of  
2 safety and efficacy of Descovy for PrEP to  
3 adolescents can be based on similar pharmacokinetic  
4 exposures to Descovy between the DISCOVER study  
5 participants and adolescents, as well as the  
6 similar mechanism of action of these drugs. We  
7 also know that HIV infection status has no relevant  
8 impact on these parameters. Taken together, these  
9 data support the use of Descovy for HIV prevention  
10 in adolescents.

11           Based on the data from the DISCOVER study,  
12 the established safety and efficacy of Descovy for  
13 HIV treatment across men, women, and adolescents  
14 and pharmacokinetic bridging, the following  
15 additional indication is proposed for Descovy.  
16 Descovy is indicated for pre-exposure prophylaxis  
17 to reduce the risk of sexually-acquired HIV in  
18 at-risk adults and adolescents weighing at least  
19 35 kilograms.

20           You will next hear from Dr. Scott  
21 McCallister, who will provide an overview of the  
22 phase 3 DISCOVER trial and the efficacy results.

1 Then Dr. Moupali Das will present the safety of  
2 Descovy for PrEP, as well as the basis for its use  
3 for HIV prevention in women and adolescents.

4 We're honored to have Dr. Rick Elion with us  
5 today. Dr. Elion has a long-standing history of  
6 providing HIV treatment and prevention services to  
7 individuals in the D.C. area for marginalized  
8 communities, and he'll provide clinical context for  
9 the results of the DISCOVER trial. I will then  
10 return to lead our responses to questions. We have  
11 Gilead team members spanning multiple disciplines  
12 to address these questions.

13 In addition, we're pleased that Dr. Peter  
14 Anderson is here today to address questions around  
15 adherence. Dr. Anderson is a professor of  
16 pharmaceutical sciences at the University of  
17 Colorado. His laboratory specializes in the  
18 assessment of drug levels in dried blood spots, and  
19 they performed nearly 4,000 dried blood spot  
20 analyses in DISCOVER as part of our adherence  
21 assessments.

22 I'd like to now welcome Scott McAllister to

1 the lectern.

2 **Applicant Presentation - Scott McCallister**

3 DR. McCALLISTER: Thank you, Diana, and good  
4 morning, everyone. I'm also an infectious disease  
5 specialist with a long history of clinical patient  
6 care and clinical research in HIV. In this  
7 section, I'll describe the DISCOVER study design,  
8 the treatment population, and the efficacy results.

9 DISCOVER is an ongoing, randomized,  
10 double-blind, noninferiority trial that enrolled  
11 both cismen and transgender women who have sex with  
12 men. As shown at the top, participants were  
13 randomized 1-to-1 to either Descovy or Truvada  
14 daily. Each of the nearly 2700 MSM or transgender  
15 women received 1 tablet of active drug and 1 dummy  
16 placebo tablet.

17 The primary efficacy endpoint analysis was  
18 time based and was conducted when all participants  
19 completed 48 weeks in the study and half had  
20 completed 96 weeks. The primary endpoint was the  
21 HIV incidence rate per 100 person-years on study.  
22 The study was blinded to investigators and study

1 participants until the final person enrolled  
2 completed 96 weeks. At the next scheduled visit,  
3 individual participants are unblinded and offered a  
4 switch to open-labeled Descovy. Unblinding is  
5 currently ongoing and not yet complete.

6 Eligibility criteria were designed to ensure  
7 that the study enrolled a population at high risk  
8 of HIV infection. All participants were required  
9 to have at least 1 of the 2 following sexual risk  
10 criteria: two or more episodes of condomless anal  
11 sex with more than one unique partner in the 12  
12 weeks before enrollment or a diagnosis of either  
13 rectal gonorrhea, rectal chlamydia, or syphilis in  
14 the 24 weeks before enrollment. All needed to be  
15 HIV and hepatitis B negative. Prior or current use  
16 of PrEP was permitted, and no washout of PrEP drugs  
17 was required.

18 DISCOVER sites were mostly urban. They were  
19 specifically chosen to be in locations with a high  
20 background HIV incidence, and all sites were  
21 required to be able to enroll people with  
22 significant sexual risk for HIV acquisition. We

1 also selected sites with the cultural competence to  
2 enroll and retain people of color and transgender  
3 women.

4           Ultimately, DISCOVER included 94 sites in 11  
5 countries in North America and Western Europe.  
6 Some were hospitals, some private practices, and  
7 some local sexually transmitted infection clinics.  
8 Each site was responsible to determine the best  
9 recruitment practice within their own community.  
10 All of those who met eligibility criteria were  
11 allowed to enroll. It was our goal to allow each  
12 person who knew themselves to be at risk of our HIV  
13 infection to participate.

14           When we designed DISCOVER, we consulted with  
15 investigators from the prior PrEP trials in MSMs.  
16 We wanted to ensure that the study included the  
17 right design elements, comparable sexual risk  
18 eligibility criteria, optimal HIV testing, and STI  
19 testing, so that our study would yield reliable  
20 results. We also discussed design issues with both  
21 site investigators and with community members in  
22 North America and Europe to ensure that the study

1 was practical and aligned with existing clinical  
2 practice.

3 Community members encouraged us to establish  
4 advisory boards for ongoing dialogue with them. As  
5 a result, three community advisory boards were set  
6 up, one that was DISCOVER specific and two that  
7 dealt with broader HIV issues in North America and  
8 the EU. We drew valuable input from these  
9 interactions during the trial, during the design  
10 phase, during recruitment, and during study  
11 conduct.

12 The primary efficacy endpoint was based on  
13 the number of HIV infections diagnosed in DISCOVER  
14 divided by person-years of exposure in the study.  
15 Noninferiority of Descovy to Truvada was assessed  
16 by an incidence rate ratio in which the HIV  
17 incidence rate in the Descovy arm was divided by  
18 the rate in the Truvada arm.

19 We derived the noninferiority margin of 1.62  
20 by pooling the incidence rates in the Truvada arms  
21 of the three prior randomized controlled trials in  
22 MSMs: iPrEx, PROUD, and IPERGAY. If the upper

1 bound around the confidence interval of the  
2 incidence rate ratio in DISCOVER was less than  
3 1.62, Descovy would be noninferior to Truvada.

4 The incidence rate ratio analysis of the  
5 primary endpoint was a robust means of evaluating  
6 the effectiveness of Descovy, ensuring that the  
7 result was due to the drugs used in the study and  
8 that the treatment population was at sufficient  
9 risk of HIV.

10 At each visit, we assessed general safety,  
11 including graded adverse events, adverse events  
12 leading to discontinuation, serious adverse events,  
13 and general safety labs. There was renal lab  
14 testing at each visit, bone mineral density testing  
15 every 48 weeks, and sexually transmitted infection  
16 testing from 3 anatomic sites also at each visit.

17 We used an analysis cascade for 6  
18 prespecified secondary safety endpoints, where  
19 previous data suggested a possible difference  
20 between the arms due to lower levels of plasma TFV  
21 in those on TAF. The safety's cascade began with  
22 changes from baseline in bone mineral density, or

1 BMD, at both the hip and spine.

2 If there were significant differences  
3 favoring Descovy on each of these, we then  
4 evaluated spillage of the specific proximal renal  
5 tubular proteins associated with plasma TFV, the  
6 beta-2 microglobulin, and retinol binding protein  
7 to creatinine ratios. Then with continued  
8 significant differences favoring Descovy, we moved  
9 to evaluate glomerular function with general urine  
10 proteins, serum creatinine, and estimated  
11 glomerular filtration rate.

12 All participants completed confidential  
13 questionnaires on an iPad at the screening visit  
14 and at all study visits. These questions inquired  
15 about the sexual behavior of each participant since  
16 their last visit, including the number of partners,  
17 the type of sex, the frequency of sex, condom use  
18 habits, and about recent study drug adherence.

19 At each visit, all participants received HIV  
20 risk reduction education, adherence support, and  
21 condoms and lubricant from site staff. In  
22 addition, opt-in/opt-out text messaging could be

1 used to remind the individual to take their study  
2 meds daily with the actual words used in the text  
3 chosen by sites and participants.

4 Adherence is a critical determinant of PrEP  
5 efficacy, so we measured it in multiple ways. We  
6 employed two subjective tests, the confidential  
7 iPad-based questionnaires and counts from returned  
8 pill bottles, both at each visit. We used one  
9 objective test, a dried blood spot collection to  
10 evaluate TFV diphosphate levels in red blood cells  
11 also at each visit. Dried blood spots provided  
12 validated analysis of chronic adherence over the  
13 8 weeks prior to the collection date, and we looked  
14 at a randomly selected subset of 540 participants,  
15 about 10 percent of the DISCOVER population.

16 In addition to the randomly selected subset,  
17 we also analyzed dried blood spots in a case  
18 control analysis of those diagnosed with HIV in  
19 DISCOVER with matching controls for each. In our  
20 case control study, we compared every individual  
21 diagnosed with HIV on study and matched them with  
22 5 uninfected controls. The matched controls were

1 specifically chosen to be geographically linked, to  
2 have similar time on the study drugs in DISCOVER,  
3 and to have comparable sexual exposure as evidenced  
4 by the on-study diagnosis of a rectal STI.

5 From the group of uninfected study  
6 participants who were a match for each case, 5 were  
7 randomly selected. Once all controls were  
8 selected, dried blood spot analyses of the TFV  
9 diphosphate level in red blood cells were tested on  
10 the date of the HIV diagnosis and also on one visit  
11 prior.

12 More than 5800 people were screened for  
13 DISCOVER; 364 did not meet eligibility criteria,  
14 including 49 who tested HIV positive; 5,399 were  
15 randomized but 6 in each arm were not treated.  
16 leaving 2694 treated in the Descovy arm and 2693  
17 treated in the Truvada arm.

18 The full analysis set included 535,335  
19 participants who were randomized, treated, and had  
20 any post-baseline data. Of those who were  
21 randomized and treated in the study, the median age  
22 was 34, 12 percent of the population or emerging

1 adults below age 25 and not yet at peak bone mass.

2 In the ratio breakdown, across the 11 North  
3 American and European countries, 84 percent  
4 self-identified as white and 9 percent as black;  
5 25 percent reported being of Hispanic or Latinx  
6 ethnicity; 74 participants, or 1 to 2 percent of  
7 the population, self-identified as a transgender  
8 woman. From responses on the confidential  
9 questionnaire, the self-reported sexual orientation  
10 was gay or homosexual in 91 to 92 percent, bisexual  
11 in 6 to 8 percent, and heterosexual in 1 percent.

12 Baseline sexual behavior data from the  
13 confidential questionnaire showed that the  
14 treatment population was at significant risk of HIV  
15 infection. 58 to 60 percent had at least  
16 2 condomless receptive anal sex partners in the 12  
17 weeks prior to study entry; 9 to 13 percent  
18 reported rectal gonorrhea, rectal chlamydia or  
19 syphilis in the 24 weeks before study entry.

20 Two-thirds of DISCOVER participants had used  
21 recreational drugs, and nearly a quarter reported  
22 binge drinking, defined as 6 or more drinks on at

1 least one occasion and occurring at least monthly.  
2 A total of 23 percent had used Truvada for PrEP in  
3 the past, and 16 to 17 percent were on it at study  
4 entry. While on study, DISCOVER participants  
5 maintained this high level of sexual behavior  
6 throughout all visits.

7 Participants averaged just under  
8 4 condomless receptive anal sex partners at  
9 baseline and continuing throughout the study,  
10 similar between the arms. They also had high rates  
11 of sexually transmitted infections; 57 percent of  
12 those on the study were diagnosed with gonorrhea or  
13 chlamydia from at least 1 of the 3 anatomic sites  
14 tested. And including syphilis, the overall rate  
15 on study for any one of these STIs range from 139  
16 to one 145 per 100 person-years in DISCOVER.

17 Overall, 42 percent of participants had a  
18 rectal STI on the study, most likely due to  
19 condomless receptive anal sex, and 16 percent had a  
20 urethral STI associated with condomless insertive  
21 sex.

22 At the time of the primary endpoint

1 analysis, 16 to 17 percent of participants  
2 discontinued study drug in DISCOVER. The most  
3 common reasons for discontinuation from study drug  
4 were participant decision or lost to follow 6 to  
5 7 percent each. Only 1 to 2 percent of study  
6 participants discontinued drug due to an adverse  
7 event, and the other reasons for discontinuation  
8 were less than 1 percent each.

9 As Diana described, the study met its  
10 primary efficacy endpoint for noninferiority. In  
11 over 8700 person-years on study across the 2 arms,  
12 a total of 22 HIV infections were diagnosed; 7 in  
13 the Descovy arm, 15 in the Truvada arm,  
14 corresponding to HIV incidence rates of 0.16 and  
15 0.34 per hundred person-years, respectively. The  
16 rate ratio, where 0.16 is divided by 0.34, is 0.47.

17 For the primary endpoint analysis, the rate  
18 ratio of 0.47 represents a 53 percent reduction in  
19 HIV incidence for the Descovy arm relative to the  
20 Truvada arm. The upper bound of the confidence  
21 interval around 0.47 is 1.15. This is lower than  
22 the 1.62 prespecified noninferiority margin that's

1 establishing the noninferiority of Descovy to  
2 Truvada for PrEP.

3 We categorized the 7 diagnoses in the  
4 Descovy arm and the 15 in the Truvada arm based on  
5 whether or not they occurred prior to study entry.  
6 Evaluating all available data and prior to  
7 unblinding, a 3-physician panel concluded that 5 of  
8 the 22 HIV diagnoses most likely occurred prior to  
9 DISCOVER study entry between the screening and the  
10 randomization visits. The 5 with suspected  
11 baseline infections are shown here in the black  
12 section at the bottom of each bar. Just above are  
13 the 17 individuals, 6 in Descovy and 11 in Truvada,  
14 who acquired HIV while on study.

15 To better understand the impact that the  
16 5 suspected baseline infections had on the primary  
17 efficacy endpoint, we went on to conduct a  
18 sensitivity analysis. By excluding the  
19 5 individuals with suspected baseline infection, 1  
20 in the Descovy arm, 4 in the Truvada arm, the  
21 incidence rate ratio in this sensitivity analysis  
22 is 0.55.

1           The confidence interval around it extends to  
2 1.48, which is still below the prespecified 1.62  
3 noninferiority margin. Therefore, even excluding  
4 the suspected baseline infections in the  
5 sensitivity analysis, the incidence rate in the  
6 Descovy arm remained noninferior to the rate in the  
7 Truvada arm.

8           We next looked at efficacy analysis by  
9 baseline subgroups. In this forest plot, the HIV  
10 incidence rates for the 2 arms are shown again at  
11 the top and just left of center. The rate ratio  
12 and surrounding 95 percent confidence interval are  
13 shown at far right. The rows of the table provide  
14 incidence rates for both demographic and baseline  
15 risk behavior subgroups.

16           For each of these subgroups, the incidence  
17 rates are low and consistent with the rates in the  
18 overall study, and the incidence rate ratios  
19 demonstrate that the effect of Descovy or Truvada  
20 was consistent with the rate ratio in the overall  
21 study across all demographic and baseline risk  
22 behavior subgroups.

1           In this diagram are genotypic resistance  
2 data of the 22 individuals diagnosed with HIV; 19  
3 had samples that could be successfully amplified  
4 and evaluated. Of these 19, only 4 had Gina  
5 genotypic resistance detected to either of the  
6 study drugs.

7           All 4 occurred in the Truvada arm. All 4  
8 were M184 mutations consistent with resistance to  
9 FTC, and all 4 occurred in those with a suspected  
10 baseline infection. Each of the 4 individuals with  
11 M184 detected were able to be successfully  
12 suppressed on ART, 3 with a Descovy-based regimen.

13           Our analysis of subjective adherence  
14 measures demonstrates that there was a very high  
15 level of adherence across the arms. With  
16 self-report from the confidential questionnaires,  
17 about 80 percent reported that they took their  
18 study meds more than 95 percent of the time across  
19 all study visits and similar across the arms. With  
20 pill counts from returned bottles of study drug,  
21 about 70 percent appeared to be using their study  
22 meds more than 95 percent of the time, also similar

1 across the arms.

2 The levels of TFV diphosphate in red blood  
3 cells from the subset of dried blood spots tested  
4 also demonstrate that there was a high level of  
5 adherence in DISCOVER for both study arms. From  
6 the nearly 4,000 dried blood spots tested in the  
7 random subset, 80 to 90 percent had TFV diphosphate  
8 levels in a range consistent with taking 4 or more  
9 tablets per week for both arms.

10 In contrast, very few, just 5 to 9 percent  
11 at any visit, had TFV diphosphate levels consistent  
12 with taking less than 2 tablets per week. In the  
13 case control analysis where the 22 HIV cases were  
14 compared to HIV uninfected controls, the dried  
15 blood spot data analysis there provides a clear  
16 explanation for the difference between those with  
17 HIV and their matched controls.

18 Low or no adherence was the most significant  
19 risk factor associated with HIV in the study for  
20 both arms. In the case control study, drug  
21 adherence as measured in dried blood spots was  
22 significantly lower among those who became infected

1 as compared to matched controls. Most cases had  
2 TFV diphosphate levels in red blood cells  
3 consistent with using study drug less than 2 doses  
4 per week, while more than 90 percent of controls  
5 had TFV diphosphate levels consistent with higher  
6 levels of adherence.

7 Finally, let's move from the TFV diphosphate  
8 levels in red blood cells, which provide us this  
9 measure of adherence, over to the levels in PBMCs,  
10 which provide a measure of efficacy. The  
11 data from dried blood spots showed a high and  
12 comparable level of adherence across both arms.

13 The levels of activated drug TFV diphosphate  
14 in PBMCs, however, were not the same across the  
15 arms. At week 4, once steady state was achieved,  
16 the median TFV diphosphate level in PBMCs was  
17 6-fold higher in the Descovy relative to the  
18 Truvada arm; 404 femtomoles per million cells in  
19 Descovy and 61 femtomoles per million cells in  
20 Truvada.

21 The amount of activated drug in the PBMCs  
22 seen in DISCOVER is consistent with established PK

1 data observed from multiple clinical studies with  
2 TAF and TDF-based regimens in chronic HIV  
3 treatment. Given that 40 femtomoles per million  
4 cells represents the 90 percent effective  
5 concentration, or EC<sub>90</sub>, of TFV diphosphate in PBMCs,  
6 98 percent in the Descovy arm were above this EC<sub>90</sub>,  
7 while only 68 percent in the Truvada arm had levels  
8 above this mark.

9 In summary, DISCOVER was conducted in MSMs  
10 and transgender women with a high baseline risk of  
11 HIV infection that was consistent over the course  
12 of the study. Over 8700 person-years, the HIV  
13 incidence rates were very low and the  
14 noninferiority of Descovy to Truvada for HIV  
15 prevention was established. Low adherence was the  
16 most significant risk factor associated with an HIV  
17 diagnosis on study.

18 While M184 mutations occurred in the Truvada  
19 arm, there was no resistance to study drugs  
20 reported in the Descovy arm. TFV diphosphate  
21 levels in PBMCs were over 6-fold higher in the  
22 Descovy arm as compared to Truvada with a

1 significantly higher proportion above the EC<sub>90</sub> for  
2 HIV protection. This PK advantage represents a  
3 potential clinical benefit of Descovy for PrEP.

4 Thank you for your attention. I'd now like  
5 to turn our presentation over to my colleague,  
6 Dr. Moupali Das, who will describe the DISCOVER  
7 safety data, and she'll provide a description of  
8 the PK bridging data in support of an indication in  
9 ciswomen and adolescents.

10 **Applicant Presentation - Moupali Das**

11 DR. DAS: Good morning, everyone. My name  
12 is Moupali Das, and I'm also an infectious disease  
13 physician. My career has been devoted to helping  
14 end the HIV epidemic by increasing virologic  
15 suppression rates and PrEP uptake. For the last  
16 six years, I've worked exclusively on clinical  
17 trials comparing the efficacy and safety of the two  
18 tenofovir prodrugs.

19 The DISCOVER trial is the largest individual  
20 trial with a single variable comparison of TAF with  
21 TDF. It offers a unique opportunity to compare the  
22 safety of TAF with TDF in the absence of underlying

1 HIV or hep B infection and without any accompanying  
2 third agents.

3           The safety and tolerability of Descovy and  
4 TAF have been thoroughly established in HIV and hep  
5 B treatment with over 26,000 person-years of  
6 experience in clinical trials and over 1.6 million  
7 person-years of clinical experience. Descovy has a  
8 superior renal and bone safety profile compared  
9 with Truvada due to the 90 percent lower plasma  
10 tenofovir levels with TAF compared with TDF. Early  
11 favorable changes in renal and bone safety  
12 biomarkers correlate with fewer clinical renal and  
13 bone adverse events over longer term follow-up.

14           The DISCOVER results are the first  
15 demonstration that these well understood renal and  
16 bone safety advantages of Descovy compared with  
17 Truvada are also true for the HIV uninfected  
18 population. There was a meeting exposure of 86 to  
19 87 weeks in Descovy and Truvada. The bone mineral  
20 substudy had 9 weeks of exposure. Both Descovy  
21 and Truvada were safe and well tolerated.

22           The type, frequency, and severity of adverse

1 events were similar between the Descovy and Truvada  
2 arms. Most adverse events were grade 1 or 2 in  
3 severity. There was a low percentage of study drug  
4 related serious adverse events or adverse events  
5 leading to discontinuation in both Descovy and  
6 Truvada.

7           During treatment, 1 person died in each arm.  
8 The most common adverse events in the DISCOVER  
9 trial were sexually transmitted infections; 6 of  
10 the 9 most common AEs were bacterial sexually  
11 transmitted infections or exposure to STIs. This  
12 is in contrast with Descovy treatment trials and  
13 may reflect increased STI screening in DISCOVER,  
14 which happened at every visit, or differences in  
15 sexual behavior among DISCOVER participants  
16 compared to the treatment trial participants, or a  
17 combination of both.

18           I will review the STI data for the next few  
19 slides and then come back to the general safety  
20 data. The rates of sexually transmitted infections  
21 were high and persistent throughout the trial.  
22 About 15 percent of participants had lab-diagnosed

1 gonorrhea or chlamydia at any of the 3 anatomic  
2 sites at baseline and throughout the study. There  
3 were no differences between Descovy and Truvada.

4 Two of the most common AEs were rectal  
5 gonorrhea and chlamydia. Approximately 10 percent  
6 of participants had rectal gonorrhea or chlamydia  
7 at baseline, and this did not change during the  
8 study. There were no differences between Descovy  
9 and Truvada. The by-visit positivity rates reflect  
10 high and persistent sexual behavior over the study  
11 with the persistent rectal STI rates reflecting  
12 continued high risk for HIV acquisition.

13 The most commonly prescribed medications in  
14 the DISCOVER trial were also different from our HIV  
15 treatment trials. Four of the seven most commonly  
16 prescribed medications are antibiotics used to  
17 treat sexually transmitted infections. More than  
18 half of the participants received azithromycin or  
19 ceftriaxone. There was a high burden of STIs,  
20 including rectal STIs diagnosed and treated during  
21 the study.

22 Returning back to general safety, the common

1 study drug related adverse events reflect the most  
2 common adverse events in the Descovy treatment  
3 trials. Twenty percent of participants in Descovy  
4 and 23 percent in Truvada had study drug related  
5 adverse events. Common related adverse events were  
6 low in frequency and similar between arms. The  
7 majority were mild GI events and headache.  
8 Laboratory abnormalities were also uncommon in the  
9 study. Grade 3 or higher lab abnormalities  
10 occurred at a low frequency and none were  
11 clinically significant.

12 In the HIV treatment trials and in the  
13 Truvada adherence subset in the iPrEx trial, the  
14 lipid-lowering effect of Truvada has been well  
15 documented. In DISCOVER, Truvada was also  
16 associated with a reduction in lipid parameters.  
17 Total cholesterol, HDL, and LDL cholesterol all  
18 declined. The magnitude of these declines is not  
19 clinically significant, whereas total cholesterol,  
20 LDL, and HDL levels were generally unchanged in  
21 participants taking Descovy.

22 Importantly, these changes resulted in no

1 difference in the total cholesterol to HDL ratios  
2 between arms, which is strongly associated with  
3 cardiovascular risks. While both Descovy and  
4 Truvada were safe and well tolerated, Descovy was  
5 significantly superior to Truvada on all 6  
6 prespecified renal and bone safety endpoints.

7 To assess the renal safety of Descovy  
8 compared with Truvada, we reviewed cases of  
9 proximal renal tubulopathy, including Fanconi  
10 syndrome, as well as all renal adverse events  
11 leading to discontinuation.

12 To specifically assess glomerular function,  
13 we measured the prespecified renal safety endpoint  
14 of serum creatinine and calculated the estimated  
15 glomerular filtration rate using the  
16 Cockcroft-Gault equation. We also evaluated total  
17 urine proteinuria by dipstick and quantitative  
18 proteinuria by the urine protein to creatinine  
19 ratio or UPCR.

20 To evaluate proximal tubular function, we  
21 looked at 2 urine tubular protein to creatinine  
22 ratios. In DISCOVER, after 8600 person-years of

1 exposure to study drug, there were no cases of  
2 proximal tubulopathy or Fanconi Syndrome on  
3 Descovy. There was one case of Fanconi Syndrome on  
4 Truvada. There were numerically fewer  
5 discontinuations due to renal AEs on Descovy  
6 compared to Truvada, 2 versus 6.

7 Descovy had significantly improved  
8 glomerular function compared with Truvada. The  
9 differences in eGFR with Descovy and Truvada were  
10 apparent as early as week 4 and continued through  
11 week 48, the prespecified time point for the  
12 assessment of secondary safety endpoints. At  
13 week 48, Descovy participants also had significant  
14 and lower serum creatinine, the prespecified safety  
15 endpoint.

16 Glomerular proteinuria was significantly  
17 lower in Descovy compared with Truvada. At  
18 week 48, 21 percent of participants on Descovy  
19 compared with 24 percent on Truvada developed  
20 dipstick proteinuria. Fewer participants on  
21 Descovy, 1 percent, compared to Truvada, 2 percent,  
22 developed clinically significant quantitative

1 proteinuria as defined by the national kidney  
2 foundation as a urine protein to creatinine ratio  
3 of greater than 200 milligrams per gram.

4 Descovy also had superior outcomes to  
5 Truvada in the two markers of proximal tubular  
6 proteinuria. Retinal binding protein and beta-2  
7 microglobulin are two low molecular weight  
8 proteins, which are freely filtered across the  
9 glomerularis and reabsorbed at the proximal tubule.  
10 Increased spillage of these proteins into the urine  
11 is a marker of increased proximal tubular  
12 dysfunction and is reflected in higher urine RBP to  
13 creatinine and urine beta-2 microglobulin to  
14 creatinine ratios.

15 On the left panel, the Truvada group had a  
16 20 percent increase from baseline in tubular  
17 proteinuria indicating increased proximal tubular  
18 dysfunction, while Descovy remained stable. On the  
19 right panel, the Truvada group had a 15 percent  
20 increase in tubular proteinuria from baseline  
21 indicating worsening of tubular function, while the  
22 Descovy group had a 10 percent decline or

1 improvement in tubular proteinuria.

2 The superior renal safety of Descovy was  
3 also demonstrated in participants who were on  
4 Truvada at baseline who switched to Descovy  
5 compared to those who remained on Truvada. The  
6 DISCOVER trial included participants taking Truvada  
7 for PrEP at baseline and did not require a washout  
8 of Truvada. There were a large number, 905 people,  
9 who were on Truvada at baseline.

10 We prespecified sensitivity analyses of the  
11 participants on baseline Truvada for key renal and  
12 bone safety endpoints. As in the overall DISCOVER  
13 population, those on baseline Truvada who switched  
14 to Descovy had improvements in renal function  
15 compared to those who remained on Truvada. The  
16 improvements in eGFR and those who switched to  
17 Descovy were apparent as early as week 4 and  
18 persisted through week 48.

19 The improvements with switching to Descovy  
20 are also present in markers of proximal tubular  
21 function. Those who switch to Descovy had  
22 significant declines in tubular proteinuria

1        indicating improved tubular function, while those  
2        who remained on Truvada had an 11 percent increase  
3        in retinal binding protein to creatinine ratio on  
4        the left and a stable beta-2 microglobulin to  
5        creatinine ratio on the right.

6                These changes again became apparent as early  
7        as week 4 and continued through week 48. Descovy  
8        was superior to Truvada on all prespecified  
9        biomarkers of renal function. This was  
10       demonstrated in both the overall population as well  
11       as in the Truvada switchers.

12               We evaluated bone safety with the bone  
13       mineral density substudy. The median age of  
14       DISCOVER participants was 34, so approximately half  
15       of the participants were still building to peak  
16       bone mass, which is achieved in the early to mid  
17       30s.

18               Descovy participants had a statistically  
19       significant increase in mean spine bone mineral  
20       density of about 0.5 percent from baseline and  
21       stable hip bone mineral density, whereas those on  
22       Truvada had statistically significant declines of

1 1 percent of both spine and hip bone mineral  
2 density from baseline through week 48. Descovy was  
3 statistically superior to Truvada in both  
4 prespecified bone endpoints.

5 Using the T scores from the Baseline BMD  
6 assessment, participants were classified into the  
7 clinically relevant categories of normal bone  
8 mineral density, osteopenia, and osteoporosis. At  
9 baseline, 27 to 29 percent of participants had  
10 either spine osteopenia or osteoporosis in the  
11 Descovy and Truvada arms. After 48 weeks,  
12 participants on Descovy had significantly less  
13 osteopenia and osteoporosis than those on Truvada.

14 As Scott showed you, there were  
15 6 prespecified secondary safety endpoints. Descovy  
16 was superior to Truvada in all 6 prespecified,  
17 alpha-controlled bone and renal safety endpoints at  
18 the week 48 endpoint. We continue to follow  
19 long-term renal and bone safety in the DISCOVER  
20 study participants.

21 Both Descovy and Truvada were safe and well  
22 tolerated. The rates of serious adverse events or

1 adverse events leading to discontinuation of study  
2 drug were low and balanced between arms. The  
3 magnitude of the differences in the early safety  
4 endpoints between arms was similar to what is  
5 observed in HIV and hep B treatment trials  
6 comparing to Descovy to Truvada.

7 This large trial confirmed that the  
8 well-established superior renal and bone safety  
9 profile of Descovy to Truvada from HIV and hep B  
10 treatment is also true in HIV prevention. The  
11 safety benefits were seen in both the people  
12 starting PrEP for the first time as well as those  
13 switching from Truvada to Descovy.

14 This is a significant development from a  
15 clinical perspective, so we can now offer a  
16 similarly efficacious but safer drug as another  
17 choice for HIV uninfected people who are simply at  
18 risk for HIV acquisition. The efficacy and safety  
19 of Descovy for ciswomen, cismen who have sex with  
20 men, and adolescents can be inferred from DISCOVER.

21 The extensive clinical experience with  
22 Descovy and Truvada for treatment and prevention

1 allows for the inference of efficacy and safety in  
2 ciswomen and adolescents. We have over 15 million  
3 person-years of clinical experience with Truvada  
4 and TDF and 1.6 million person-years with Descovy  
5 and TAF in HIV and hep B treatment.

6 We have over 108,000 person-years in Truvada  
7 for PrEP and 6500 person-years for Descovy for PrEP  
8 from the DISCOVER trial. Both Truvada and Descovy  
9 are highly effective for treatment and prevention.  
10 Efficacy is driven by tenofovir diphosphate in  
11 peripheral blood mononuclear cells or PBMCs. In  
12 contrast, safety is driven by plasma tenofovir.  
13 The 90 percent lower plasma levels with Descovy  
14 compared with Truvada is associated with an  
15 improved bone and renal safety profile.

16 The PK of Descovy or Truvada is independent  
17 of intrinsic and in extrinsic factors. This means  
18 that the PK of plasma tenofovir and tenofovir  
19 diphosphate in PBMCs is not affected by sex at  
20 birth, current gender identity, or sexual  
21 orientation. HIV infection status also does not  
22 affect PK.

1           The active moiety for both Truvada and  
2       Descovy associated with both HIV treatment and  
3       prevention efficacy is tenofovir diphosphate in  
4       PBMCs. Tenofovir diphosphate levels are comparable  
5       with Descovy in the MSM and transwomen in DISCOVER  
6       on the left and Descovy in ciswomen and cismen.

7           In contrast, the tenofovir diphosphate  
8       levels are lower with Truvada on the right.  
9       Tenofovir diphosphate levels are 4 to 7-fold higher  
10      with Descovy than with Truvada, and this is  
11      consistent with findings in prior trials. Efficacy  
12      is high in both women and men on Descovy-based  
13      regimens for HIV treatment as it is with Truvada.  
14      Virologic suppression rates are similar on Descovy  
15      and Truvada-based regimens for HIV treatment and  
16      similar in women and men.

17           The key metabolite for both Truvada and  
18      Descovy associated with safety is plasma tenofovir.  
19      Plasma tenofovir with Descovy is similar in women  
20      with HIV and in HIV uninfected female volunteers.  
21      The PK is independent of HIV status. Plasma  
22      tenofovir is 10-fold higher with Truvada shown here

1 in women with HIV on the right. Women with HIV  
2 have improved renal safety on Descovy compared with  
3 Truvada-containing regimens for HIV treatment.

4 In 519 women who were switched from Truvada  
5 to Descovy or remained on Truvada, there were  
6 significant improvements in both glomerular  
7 function on the left and proximal tubular function  
8 on the right through 96 weeks in the women switched  
9 to Descovy. These renal improvements are  
10 consistent with the DISCOVER results in those on  
11 baseline Truvada who switched to Descovy.

12 Women on Truvada-containing regimens who  
13 switched to Descovy also had clinically significant  
14 improvements in osteopenia and osteoporosis within  
15 48 weeks. At baseline, a third of women on  
16 Truvada-based regimens for HIV treatment had  
17 osteopenia or osteoporosis. Women who switched to  
18 Descovy had less spine osteopenia and less  
19 osteoporosis at week 48 compared to those who  
20 continued on Truvada. These results were  
21 statistically significant.

22 Descovy is also an efficacious and safe

1 treatment for HIV in adolescents. Descovy is  
2 approved for HIV treatment in adolescents weighing  
3 at least 35 kilograms in combination with third  
4 agents and in 3 Descovy-containing, single-tablet  
5 regimens. Descovy has similar renal and bone  
6 safety benefits compared with Truvada in  
7 adolescents with HIV. Truvada has been approved  
8 for PrEP in adolescents weighing at least  
9 35 kilograms since 2018, based on the extrapolation  
10 of efficacy from adults.

11 Tenofovir diphosphates and PBMCs is the  
12 active moiety associated with both HIV treatment  
13 and prevention efficacy. Tenofovir diphosphate  
14 levels are similar in adults in DISCOVER and in  
15 adults and adolescents with HIV. As we saw before,  
16 HIV infection status does not affect PK, so we  
17 would expect similarly high levels in PBMCs in  
18 adolescents if they were taking it for PrEP.

19 Fifty adolescents who initiated a  
20 Descovy-containing regimen for HIV treatment were  
21 also evaluated. The mean age in the study was 15  
22 years and over half the participants were female.

1 Descovy was highly efficacious in adolescence for  
2 HIV treatment. Efficacy was similar in adolescent  
3 girls and boys.

4 Plasma tenofovir is associated with safety.  
5 With Descovy, the plasma tenofovir levels in adults  
6 without HIV and adults and adolescents with HIV are  
7 similar across all three populations shown on the  
8 left. Plasma tenofovir is 10-fold higher with  
9 Truvada in adolescents with HIV, which is  
10 consistent with results from prior studies.

11 Truvada has adverse effects on bone mineral  
12 density in adolescents on Truvada for PrEP or HIV  
13 treatment. Importantly, due to the 90 percent  
14 lower plasma tenofovir concentrations with Descovy,  
15 there is no such impact on bone growth.

16 Bone mineral density in the two key  
17 pediatric metrics of total body less head and spine  
18 increased through week 48 with a 0.19 percent  
19 increase in total body and at 3.3 percent increase  
20 in spine. Adolescent participants continue to  
21 build bone mineral density similarly to an age-,  
22 sex- and race-matched population.

1 Descovy is noninferior to Truvada in HIV  
2 treatment and prevention efficacy. The tenofovir  
3 diphosphate levels in PBMCs are comparable in the  
4 men and transwomen in DISCOVER, in ciswomen, and in  
5 adolescents. Descovy is superior to Truvada in  
6 renal and bone safety.

7 Plasma tenofovir is 90 percent lower with  
8 Descovy than Truvada and comparably low in  
9 DISCOVER, ciswomen, and adolescents. The efficacy  
10 and safety of Descovy for PrEP can be inferred for  
11 ciswomen and adolescents. Taken together, the  
12 comparable exposures and the extensive efficacy and  
13 safety data support the purposefully inclusive  
14 indication.

15 We have planned multiple effectiveness  
16 studies of Descovy for PrEP in a diverse range of  
17 populations, including ciswomen and adolescents.  
18 We considered numerous approaches to studying the  
19 efficacy of Descovy in women in 2015 when we were  
20 designing the DISCOVER trial. Ciswomen were not  
21 included in discover because the HIV incidence rate  
22 in the sites where DISCOVER was conducted is about

1 13-lower in women with high risk for HIV compared  
2 with the MSM with high risk in those locations.

3 With respect to doing a dedicated trial in  
4 ciswomen, there are three generally accepted  
5 approaches to randomized clinical trials for  
6 efficacy. A placebo-controlled trial with Descovy  
7 versus placebo is not ethical, as Truvada is  
8 approved and highly effective for PrEP in adherent  
9 women.

10 A superiority trial for Descovy over Truvada  
11 was also not reasonable as both are oral daily  
12 pills differentiated, primarily, although not  
13 exclusively, on safety. Lastly, we considered a  
14 noninferiority trial. Unlike DISCOVER where we  
15 pulled treatment effects from three randomized  
16 control trials with similar efficacy in MSM and  
17 transwomen, the 5 randomized controlled trials in  
18 women lacked a consistent treatment effect from  
19 which we could conduct a defensible noninferiority  
20 margin.

21 Using only the two trials with the highest  
22 efficacy in women taking Truvada, we were able to

1 estimate that a noninferiority trial would require  
2 enrollment of about 22,000 women in the high  
3 incidence regions. This would require  
4 approximately 8 to 10 years to conduct.

5 The design of the DISCOVER trial was not  
6 amenable to the inclusion of adolescents. Truvada  
7 was not approved for adolescents until 2018, so we  
8 would be comparing this safety and efficacy of two  
9 investigational agents. More importantly, we knew  
10 from data with Truvada that adolescents require a  
11 higher visit frequency to maintain adherence and  
12 may benefit from age appropriate targeted  
13 interventions to maximize recruitment and retention  
14 in clinical trials.

15 The efficacy and safety of Descovy for PrEP  
16 in women and adolescents can be inferred from the  
17 totality of evidence for Truvada and Descovy for  
18 HIV prevention and our extensive safety database  
19 from HIV treatment. Clinical data are now needed  
20 to inform providers and individuals at risk for HIV  
21 regarding the clinical effectiveness of Descovy for  
22 PrEP in ciswomen and adolescents.

1           We are dedicated to generating these data,  
2           and we will be supporting a number of studies in  
3           over 3400 ciswomen and adolescents in the United  
4           States and in Africa. Key effectiveness research  
5           questions include the evaluation of the safety of  
6           Descovy for PrEP in pregnant and breastfeeding  
7           women and how the improved safety tolerability and  
8           smaller size of Descovy could improve PrEP uptake  
9           and persistence.

10           We are strongly committed to understanding  
11           how having an additional choice for PrEP with  
12           Descovy, which has an improved renal and bone  
13           safety profile and pharmacologic properties  
14           consistent with an earlier and longer duration of  
15           protection from HIV, can help address our shared  
16           goals of increasing PrEP uptake and helping to end  
17           the HIV epidemic.

18           Thank you. I'm now pleased to invite  
19           Dr. Rick Elion to talk about the clinical impact of  
20           the DISCOVER trial.

21                           **Applicant Presentation - Richard Elion**

22           DR. ELION: Good morning. My name is

1 Dr. Rick Elion. My conflicts are I do research  
2 currently with Gilead, ViiV, and Proteus. I'm a  
3 member of an advisory panel for Gilead and ViiV.  
4 I'm on the speakers bureau of Gilead, ViiV, and  
5 Janssen. I have no stock or financial interest in  
6 these proceedings.

7 I have been active in the care of HIV  
8 patients since I left residency in 1983. I began  
9 in Brooklyn and moved to the East Village in  
10 Manhattan in 1985, at the time of the first HIV  
11 test in April of that year, and I've been  
12 continuously at the front lines of caring for HIV  
13 patients and seeking solutions and improvements in  
14 care for over 30 years. I've watched countless men  
15 and women die in my first 10 years of practice.

16 Advances in treatment and now prevention  
17 have transformed what was once a harrowing job to  
18 one of immense satisfaction. I'm currently  
19 director of research at the Washington Health  
20 Institute that serves a low-income population in  
21 the District and a clinical professor of medicine  
22 at George Washington University. I've been the

1 director of research at Whitman Walker Health,  
2 where we were a site for one of the first PrEP  
3 demonstration projects, and I have supervised  
4 hundreds of patients starting PrEP since 2013.

5 I also work at the Department of Health in  
6 Washington, D.C. in the Wellness Program, which is  
7 the Center for Caring for Those with Sexually  
8 Transmitted Infections and providing PrEP and  
9 research and methods to improve HIV prevention in  
10 the District. I also continue to follow patients  
11 at the Washington Health Institute, some of which I  
12 have cared for, for 20 years or longer. I'm  
13 grateful and honored to have the chance to share my  
14 perspective on why Descovy is an important addition  
15 to our prevention toolbox.

16 It's estimated that approximately 90 percent  
17 of all new infections are coming from people who  
18 either don't know their diagnosis, or they've been  
19 diagnosed and are not engaged in care, or not  
20 virologically suppressed. While treatment as  
21 prevention is very successful at preventing new  
22 infections, the bulk of new infections will not be

1 prevented with just treatment alone.

2 We need multiple options for patients to  
3 choose their ideal method of prevention, as when  
4 consumers have more choices, it leads to greater  
5 engagement. We will not likely have a vaccine soon  
6 to protect uninfected individuals, so PrEP is  
7 critical to help us cut down the rate of new  
8 infections.

9 Prevention is much broader than just a pill  
10 to protect against HIV. They have a variety of  
11 options, which allow each person to choose what's  
12 right for them. Choice is critical for patients,  
13 as they're much more comfortable and committed to  
14 the choices that they make rather than being told  
15 what to do.

16 Biomedical interventions including treatment  
17 as prevention and PrEP are among the most useful.  
18 Treatment as prevention has been fundamental in  
19 helping the decline of 18 percent of new cases in  
20 the United States. It's the future synergies of  
21 these approaches for treatment for HIV infected  
22 individuals and PrEP for uninfected individuals.

1           The analysis shown here looked at the change  
2           in new diagnoses of HIV over a 5-year period in  
3           states grouped by PrEP use. This data is  
4           controlled for rates of virologic suppression and  
5           in states with low PrEP use as defined as 3 percent  
6           on PrEP. You can see about a 1 percent increase in  
7           annual HIV diagnosis.

8           This can be compared to the high PrEP use  
9           group with 11 percent on PrEP where you see almost  
10          a 5 percent reduction in new cases. These rates of  
11          PrEP utilization are still quite low considering  
12          the risk profiles of patients in these communities  
13          and could be greater if there were greater adoption  
14          of PrEP.

15          This CDC report makes clear that communities  
16          at need are receiving PrEP. This slide  
17          demonstrates, however, the imbalance between the  
18          potential need for PrEP in certain communities and  
19          the actual use of PrEP. Dawn Smith, who's here  
20          this morning, and colleagues reported on the  
21          disparities between the potential members of  
22          various populations that would qualify for PrEP

1 versus those who are using PrEP.

2           These differences are staggering in the  
3 communities in need as can be seen in this life.  
4 Gross differences exist but only a fraction of  
5 these communities are benefiting from PrEP, ranging  
6 from racial disparities for blacks and Hispanic to  
7 women as well. Though not shown here, certainly  
8 adolescents , those from 15 to 25 years of age, who  
9 are sexually active are also facing these same  
10 disparities.

11           We know that Truvada for PrEP is efficacious  
12 in adolescents with adequate adherence. DISCOVER  
13 demonstrated efficacy in cisgender and transgender  
14 women. Descovy pharmacology is consistent across  
15 different ages. The PK profile of Descovy could  
16 have some advantages for adolescents as reflected  
17 by the higher exposures that are achieved and the  
18 higher intracellular drug levels that stay elevated  
19 longer after missed doses.

20           This notion of forgiveness of suboptimal  
21 adherence is critical for this population. Aside  
22 from the potential benefits of a better PK profile,

1 Descovy will be a safer medication for a population  
2 that's actively building bone mass into their early  
3 30's. They are depositing bone as part of their  
4 normal growth, and the bone mineral density loss  
5 with Truvada could potentially have a lasting  
6 effect on adolescents, who after using Truvada may  
7 not ever reach peak bone mass.

8           In this slide, we use the notion of a Z  
9 score. A Z score compares your bone density to the  
10 average values for a person of your same age and  
11 gender. A low Z score below 2 is a warning sign  
12 that you have less bone mass and/or may be losing  
13 bone more rapidly than expected for someone of your  
14 age.

15           Consideration of Z scores, which  
16 standardized bone mineral density for age, race and  
17 sex, is most important during adolescence when bone  
18 mineral density variability increases. Z scores  
19 are stable over at least three years during periods  
20 of rapid bone accrual. Persistent Z score decline,  
21 which you can see here, after stopping PrEP,  
22 especially in the younger participants, is a

1 concerning finding of these analysis.

2 The Z scores for individuals on Truvada for  
3 PrEP declined for both spine, hip, and total body  
4 during the 48-week period of PrEP, and then recover  
5 in a comparable time period but not back to  
6 baseline after at least 48 weeks of observation.

7 The clinical significance of this is  
8 two-fold. The first is that the bone mineral  
9 density based on the Z score does not recover to  
10 baseline 48 weeks after PrEP has been discontinued,  
11 suggesting that there is some insult to bone  
12 deposition that does not fully recover. Second,  
13 the insult is worse for those 15 to 19 who are more  
14 actively depositing bone.

15 TAF on the other hand has not been shown to  
16 have this impact on bone as reflected in  
17 HIV-positive adolescents on treatment. It is a  
18 better choice, therefore, for adolescents.  
19 Offering them a medication that will allow their  
20 bones to grow in a normal fashion is an important  
21 consideration in selecting the best medicine for  
22 HIV prevention for adolescents.

1           It's equally important for women. I  
2 previously mentioned the PK advantage for  
3 adolescents. The PK data that were presented  
4 earlier reflect a higher intracellular level of TAF  
5 in the PBMCs, and hence, a longer period that these  
6 levels stay above the threshold of efficacy, 16  
7 days versus 10 days. This represents possibly a  
8 significant difference between TAF and TDF if we  
9 can accept the assumption that PBMCs have higher  
10 drug levels and had been correlated with levels of  
11 protection. This knowledge about HIV prevention  
12 continues to evolve.

13           The DISCOVER study has demonstrated that the  
14 failure of TAF to be present in higher tissue  
15 levels for men was not a detriment to the overall  
16 efficacy. This efficacy was likely driven by the  
17 higher drug levels in the various components of the  
18 PBMCs. The higher levels and the subsequent longer  
19 time, until those levels fall below the threshold  
20 of effectiveness, could portend a more forgiving  
21 regimen and merit further study.

22           But forgiveness of missed or late doses

1       could be a significant advantage for TAF/FTC and  
2       provide a clinical advantage for those who don't  
3       take their pills every day. This would be very  
4       important for both adolescents and for women who  
5       historically have had a greater percentage of  
6       failures of PrEP due to poor adherence.

7               PrEP with Truvada has already been approved  
8       for women based on the studies seen in this slide  
9       that show comparable efficacy to men when adequate  
10      adherence is maintained. VOICE and FEM-PrEP show  
11      poor efficacy when adherence was equally deficient.  
12      Women make up approximately 19 percent of new  
13      infections and have a great deal of unsafe exposure  
14      through sexual contact.

15              Ninety-three percent of HIV negative women  
16      reported having vaginal sex without a condom and  
17      26 percent reported having anal sex.. Women  
18      therefore make up an important part of the  
19      population for controlling HIV infection and are  
20      underrepresented in their low use of PrEP. As of  
21      2015, only 2 percent of women who were eligible for  
22      PrEP were on PrEP.

1           I work with colleagues at the Washington  
2 Hospital Center in the Department of Health in the  
3 District of Columbia on engaging women in PrEP in  
4 our STI program, known as the Wellness Clinic, and  
5 the Family Planning Program at Washington Hospital  
6 Center. We have screened nearly a thousand women  
7 who are at high risk through their sexual  
8 practices, and only less than 1 percent have opted  
9 to initiate PrEP despite a vigorous program using  
10 videos, peer counseling, free medications, and peer  
11 support. Despite our numerous efforts to explain  
12 and encourage the adoption of more tools for HIV  
13 prevention for women, we have been lagging behind.

14           This data of HIV incidence from  
15 demonstration projects show the comparable rates of  
16 new infections in men and women. There should be  
17 little doubt that PrEP with Truvada works equally  
18 well in men and women when adherence is  
19 appropriate. These low rates of seroconversion  
20 demonstrate real-world efficacy. There's no data  
21 to suggest that this efficacy is different between  
22 genders when adherence is similar.

1           These data from real-world experiences  
2 support the fact that women benefit in the same  
3 fashion as men with PrEP, with Truvada in the real  
4 world, not just in clinical trial settings.  
5 However, as mentioned earlier, women have not  
6 adopted PrEP in significant number.

7           The reasons for this are complex and involve  
8 multiple issues. This study of African Americans,  
9 both men and women, demonstrate some of these  
10 challenges. Denial of risk is a critical issue for  
11 women, as well as fear of side effects and trust  
12 that these treatments will actually work.

13           Other surveys have pointed out that mistrust  
14 of providers; stigma; fear of being ousted as  
15 needing HIV protection; partner notification and  
16 lack of support from one's partner; cost; and  
17 access to medicine remain key drivers for women's  
18 reluctance to start PrEP. There are multiple  
19 reasons in the decision-making exercise by women in  
20 adopting HIV prevention, so anything we can do to  
21 lessen this burden might help women make a better  
22 informed decision.

1           The safety of TAF versus TDF regarding bone  
2 demineralization is clear. There are clinical  
3 consequences as reflected in higher risk of  
4 fracture in the treatment population on Truvada.  
5 These differences in bone mineral density could  
6 potentially be even more important in women.

7           Bone mineral density in women can be  
8 impacted by age and hormonal status. Approximately  
9 1 in 2 women over the age of 50 will break a bone  
10 because of osteoporosis. A woman's risk of  
11 breaking a hip is equal to her combined risk of  
12 breast, uterine, and ovarian cancer. HIV-positive  
13 women have a 50 percent higher risk of osteopenia  
14 at age 50 than men at a comparable age.

15           Descovy is a safer alternative for women  
16 than Truvada who are at any risk for issues related  
17 to bone health. Certainly in treatment settings,  
18 I've switched patients on Truvada to TAF-containing  
19 regimens to alleviate any concerns I would have or  
20 they would have about their bone health.

21           We know that Truvada for PrEP is equally  
22 effective in men and women. We know that PBMC

1 levels have been associated with efficacy for both  
2 HIV treatment and HIV prevention. There is no  
3 correlate of protection established for tissue  
4 levels, and only modest efficacy for topical  
5 regimens that may provide lower levels in PBMCs, as  
6 been mentioned already.

7 The low TFV tissue levels in men were not  
8 predictive of the success seen in DISCOVER and  
9 supports the notion that PBMC levels provide a  
10 correlate of protection. PBMC drug levels are  
11 similar for men and women and higher for Descovy in  
12 both men and women. And since the PBMC compartment  
13 is likely a significant predictor of efficacy, then  
14 women would have similar levels of protection as  
15 their male counterparts.

16 The key issues at this hearing are based on  
17 the evaluation of Descovy for PrEP and whether the  
18 indication should extend beyond the participants in  
19 the DISCOVER trial. There's a history of  
20 conflicting data regarding the role of tissue  
21 levels in protecting against HIV acquisition versus  
22 the role of systemic protection through components

1 of the blood. This is obviously one of the key  
2 questions before the committee today, establishing  
3 efficacy and safety in HIV prevention for all  
4 communities.

5 The data from the DISCOVER trial  
6 demonstrated that systemic protection drives  
7 efficacy in MSM and transgender women. There is an  
8 established correlate of protection for the levels  
9 of drug in PBMCs and iPrEx, and we see higher  
10 levels in PBMCs with Descovy and lower levels in  
11 rectal tissue. Yet, the point estimate in DISCOVER  
12 showed a lower rate of infection on Descovy.

13 We do know that Descovy was safer in men and  
14 transgender women, and we do know that there are  
15 improvements in safety with TAF versus TD as well,  
16 and we can debate whether these improvements will  
17 convey a significant clinical benefit. I believe  
18 they do convey a significant benefit from a safety  
19 perspective for both adolescents and women, as  
20 based on the data that has been shown today.

21 The differences in PK between TAF and TDF  
22 could be a significant differentiator between the

1 two options for PrEP, and the improved profile seen  
2 with TAF might improve outcomes by mitigating  
3 suboptimal adherence. This evidence supports the  
4 extension of the efficacy data from DISCOVER to  
5 women and to adolescents.

6 Further, at the end of the day, as a  
7 clinician, counseling men and women about the need  
8 for HIV prevention and PrEP, I can't stress enough  
9 how detrimental it would be to give men a choice of  
10 a safer medicine but not offer the same choice to  
11 ciswomen.

12 Ciswomen should have the same options that  
13 would be available to cismen and transwomen. They  
14 should not have to wait for a separate study to  
15 prove efficacy and safety in ciswomen that can take  
16 at least four years to result in approval for TAF  
17 or PrEP. Please at least allow women to have that  
18 choice. Let them decide if the safety advantages  
19 outweigh the concerns about efficacy.

20 There may be different opinions about the  
21 level of certainty that disclosure will work  
22 equally well in both sexes, and there is reasonable

1       certainty, based on the success with Truvada for  
2       HIV prevention, to extend this certainty from the  
3       male and transgender women in DISCOVER to HIV  
4       negative women and adolescents.

5               I am certain that if women and adolescents  
6       don't have that choice and are told they can't use  
7       a safer medicine that would have potentially been  
8       approved for men, it will be seen as a signal of  
9       uncertainty by these populations. They are likely  
10      to feel left behind, and it will not lead to  
11      increased engagement and use of HIV prevention. I  
12      hope we don't give those vulnerable populations  
13      that message and do allow them the option to choose  
14      what will be best for them.

15              I have taught clinicians in Uganda, Kenya,  
16      and Rwanda for the last five years, and these  
17      clinicians also look to the U.S. and the FDA for  
18      recommendations about indications for HIV  
19      medications. Providing an effective and safe  
20      medication for women in Africa, where women make up  
21      over half the cases worldwide, is fundamentally  
22      important, so these decisions today have

1       implications not just in the United States,  
2       potentially.

3               For the last 30 years as a clinician, my  
4       role has been to explain to patients their  
5       therapeutic options and help them make the best  
6       decisions for themselves. Please allow me to keep  
7       doing my job of guiding and helping patients to  
8       make the best decision and don't take the choice  
9       out of our hands. The totality of the evidence and  
10      the favorable benefit-risk profile of Descovy  
11      support making this drug available to all those in  
12      need. Thank you.

13              DR. BADEN: Thank you. I'd like to thank  
14      the applicant for a very thorough presentation of a  
15      tremendous amount of data.

16              Before we have clarifying questions to the  
17      presenters, we'll take a 10-minute break. Panel  
18      members, please remember there should be no  
19      discussion of the meeting topic during the break  
20      amongst yourselves or with any members of the  
21      audience. We will resume at 10:25. Thank you.

22              (Whereupon, at 10:14 a.m., a recess was

1 taken.)

2 **Clarifying Questions**

3 DR. BADEN: We will now resume session. If  
4 everyone can please take your seats, we have little  
5 time and much ground to cover. We have about 50  
6 minutes for clarifying questions for the  
7 applicant's presentation. We may not complete all  
8 of the clarifying questions, in which case we will  
9 then resume after lunch, after we have a chance to  
10 have the agency's presentations.

11 In the clarifying question process, for  
12 those of you who are new to joining us, what I'd  
13 like to do is to try to build on themes. I really  
14 asked for committee members to please use the honor  
15 system in how we do the clarifying question  
16 process.

17 When we start, if you are interested in  
18 asking a question, signal Lauren or I. We'll add  
19 you to the list. If a question is asked and there  
20 is a follow-on that builds on the theme, I would  
21 very much like to build on the theme. Please take  
22 your card, turn it on the side, and that will

1 indicate you want to build on the theme so that we  
2 can have a series of questions on the same topic  
3 and not be bouncing around with every other  
4 question, going back and forth between topics.

5 I just asked the committee members to really  
6 build on a theme and not have that -- a way so you  
7 can ask another question faster. We'll try very  
8 hard to get through all of the questions as quickly  
9 as possible, but I would like to, as much as  
10 possible, build on themes because I think that's  
11 more efficient and more effective.

12 We will start with our member on the phone.  
13 We'll start with the first clarifying question.

14 MS. LUPOLE: Yes, sir.

15 DR. BADEN: Please go ahead.

16 MS. LUPOLE: The question is, what, if any,  
17 are the long-term effects on bone density and renal  
18 [indiscernible] related to [indiscernible]  
19 adherence and failure?

20 DR. BRAINARD: I'm going to ask Dr. Moupali  
21 Das to come to the podium and speak to the longer  
22 term bone and renal effects of Truvada and Descovy

1 use. I believe that was your question. We'll  
2 start there. If you have an additional question,  
3 we'll take it from there.

4 MS. LUPOLE: Yes, ma'am. Basically, the  
5 failure to adhere and multiple incidences,  
6 occurring multiple incidences.

7 DR. BRAINARD: The failure to what?

8 MS. LUPOLE: [Indiscernible - feedback]

9 DR. BRAINARD: The failure to adhere. Okay.

10 So we'll present the safety data first in  
11 terms of the long-term effects, and then we'll talk  
12 about adherence and how adherence is related to  
13 efficacy.

14 DR. BADEN: And to our colleague on the  
15 phone, if you can go on mute, as we're getting  
16 feedback. Thank you.

17 DR. DAS: The bone mineral density  
18 biomarker, and the renal tubular biomarkers, and  
19 the glomerular function biomarkers chosen for  
20 evaluation in DISCOVER are associated with  
21 clinically meaningful differentiation between  
22 Descovy and Truvada over the long term. First

1 we'll look at bone, and then we'll look at renal.

2 Slide 1 up, please. The early declines in  
3 bone mineral density between weeks 24 and 48 widen  
4 over time through 3 years of follow-up in a  
5 representative example of hip BMD from 2 pooled  
6 clinical trials of Descovy- and Truvada-based  
7 regimen in HIV treatment.

8 On the right, you can see that that  
9 separation in the BMD curves is associated with  
10 clinically meaningful increase in discontinuations  
11 due to bone adverse events. This is over a 3-year  
12 time period. We have longer duration of data from  
13 the HIV treatment literature.

14 Slide 2 up. This is an analysis from the  
15 EuroSIDA cohort with 619 fractures in over 86,000  
16 person-years of follow-up. What you see here in  
17 the multivariate analysis of fracture risk, which  
18 was adjusted for demographics, HIV-specific  
19 variables, and comorbidities, is having ever been  
20 on Truvada -- excuse me, TDF versus never being on  
21 TDF was associated with a 40 percent increase of  
22 fracture risk. Being currently on TDF versus never

1 being off of it was associated with a 25 percent  
2 risk. You may ask what does this mean for people  
3 on PrEP?

4 Slide 3 up. This is data from Chou, et al.,  
5 published in JAMA earlier this year in terms of a  
6 pooled meta-analysis of PrEP trials that was done  
7 to support the U.S. Services Preventative Task  
8 Force Recommendation with a grade A for PrEP for  
9 HIV prevention. Here we see both TDF trials and  
10 Truvada trials. The duration of follow-up in these  
11 trials was significantly shorter than what we have  
12 in the treatment literature, however, there was an  
13 increased trend towards fractures in those  
14 participants receiving TDF or Truvada.

15 Now we'll switch to renal discontinuations  
16 in renal tubular biomarkers. Slide 1 up. A  
17 similar pattern exists for the 2 tubular markers,  
18 which are early markers of proximal tubular  
19 dysfunction. There are early changes as early as  
20 week 4, and the lines separate over time with  
21 longer-term follow up through week 48 and week 96.  
22 They continue to separate through week 144.

1           On the right-hand side, you can see that  
2 there were no discontinuations on people on  
3 Descovy-containing regimens, that the cumulative  
4 effect of tenofovir toxicity is evidenced by  
5 increasing adverse events from renal causes leading  
6 to discontinuations in a step-wise fashion through  
7 week 48 through week 144.

8           With respect to how this is relevant for  
9 people with PrEP, we turn again to Chou, et al's  
10 meta-analysis from JAMA earlier this year; slide 3  
11 up. Here we see that either TDF or Truvada PrEP is  
12 associated with an increased risk of renal AEs. In  
13 summary, we chose these biomarkers because we were  
14 aware of their association with clinical meaningful  
15 differentiation in terms of renal and bone safety  
16 over a longer term follow-up, and we continue to  
17 follow participants in DISCOVER to follow them long  
18 term.

19           DR. BRAINARD: With respect to the adherence  
20 question, I'll say that there have been multiple  
21 clinical trials, as well as real-world data sets,  
22 demonstrating the close correlation between

1 efficacy to Truvada for PrEP and outcome.

2 Slide 1 up, please. This figure  
3 demonstrates that across multiple different  
4 clinical trials and real-world data sets, the  
5 higher the adherence within the study or within the  
6 subanalysis within the trial, looking at adherent  
7 participants based on plasma tenofovir levels or  
8 intracellular drug levels, the higher the efficacy  
9 with respect to risk reduction for HIV acquisition.

10 DR. BADEN: If I may, on the  
11 bone -- Ms. Lupole, do you have any follow-on  
12 questions? If not, we'll have some follow-on in  
13 the room.

14 (No response.)

15 DR. BADEN: Dr. Elion on slide 105 showed  
16 TDF and adolescent bone development. Do you have  
17 similar data for TAF and adolescent bone  
18 development?

19 DR. BRAINARD: I'll ask Dr. Moupali Das to  
20 review the data we have with TAF-containing  
21 regimens in adolescents.

22 DR. DAS: First, I'll show you the data in

1 adolescents with HIV. Slide 1 up. Descovy or TAF  
2 does not have the same impact on bone mineral  
3 density as does Truvada. Here is bone safety in  
4 adolescents with HIV. You can see both that the  
5 spine and total body less head continued to  
6 increase and grow, and that there are minimal  
7 changes in the Z scores, which reflect age, race,  
8 and gender-matched populations.

9 In the DISCOVER study, we included people  
10 who were 18 and older. The age range was 18 to 76,  
11 however, we did look at the bone mineral density in  
12 participants stratified by age less than 25.

13 Slide 2 up. This comparative data between  
14 Descovy and Truvada in the participants less than  
15 25 years on the left with spine and in the middle  
16 greater than 25 years with spine. You can see that  
17 the participants on Descovy continue to have the  
18 same amount of increase in bone mineral density,  
19 whereas those on Truvada had significant declines,  
20 which is particularly relevant for this population.  
21 Similar trends were observed with hip in terms of  
22 continued growth on Descovy or stable on Descovy

1 but declines on Truvada.

2 This is consistent with the findings in PrEP  
3 that Dr. Elion showed.

4 DR. BADEN: Would these data -- compared to  
5 age-matched controls, HIV uninfected, not on a  
6 tenofovir compound, is the bone development on TAF  
7 equal or is there a difference? Because comparing  
8 it to tenofovir TDF, one may accept the decline and  
9 say the decline is not as bad. How does it compare  
10 to age-matched controls on none of these medicines?

11 DR. DAS: If we go back to slide 1, these  
12 are participants with HIV, so there is that  
13 consideration. But this is people who are on  
14 Truvada, and you're asking about participants on  
15 TAF.

16 DR. BADEN: Persons on TAF, and I'm  
17 interested in the TAF comparison to bone  
18 development in healthy age matched-controlled  
19 children not on a tenofovir compound, so that the  
20 bone development of a 20 year old on TAF and off  
21 TAF is not different.

22 DR. DAS: Okay. In this slide, because we

1 don't have any TAF data in adolescents without  
2 HIV -- this is TAF data in adolescents with  
3 HIV -- the dotted lines are the Z scores, which are  
4 matched by age, race and gender for the population.  
5 You can see in the dotted lines between zero and  
6 week 48, there's really no difference in the blue  
7 dotted-line Z score, which is a spine Z score, and  
8 the pink dotted-line Z score, which is total body  
9 less head.

10 DR. BADEN: And those would then be  
11 age-matched control unaffected?

12 DR. DAS: Yes.

13 DR. BADEN: That's what I thought you said.  
14 I just wanted that crystal clear --

15 DR. DAS: I'm sorry I didn't clarify that,  
16 yes.

17 DR. BADEN: -- that as best as we can tell,  
18 there is no abrogation of normal bone development,  
19 as best as you can tell, realizing they're HIV  
20 infected; otherwise they wouldn't be on this for a  
21 long term.

22 DR. DAS: Exactly. Thank you.

1 DR. BADEN: Thank you.

2 Did Dr. Goetz or Awni have a follow-on  
3 question?

4 DR. GOETZ: My follow-up was related to the  
5 adherence question rather than bone.

6 DR. BADEN: Please?

7 DR. GOETZ: The previous slide, the  
8 backup 1232, showed the relationship between  
9 adherence and efficacy. One of the considerations  
10 is the relationship between adherence and efficacy  
11 on Truvada-containing regimens, or TDF-containing  
12 regimens, the same in women as in men. I think  
13 that helps inform our thoughts as to where the  
14 local tissue concentrations are important.

15 So looking at the VOICE/FEM-PrEP versus  
16 iPrEP [ph] populations, I wonder if you can go into  
17 more detail as to regards to how levels of  
18 adherence, which then presumably correlate with  
19 PBMC concentrations, correlate with levels of  
20 protection in women versus men.

21 DR. BRAINARD: The levels of adherence  
22 measured across these studies varied. They weren't

1 all uniformly assessing adherence through the same  
2 mechanism. However, the association between  
3 adherence and efficacy by these measures, whether  
4 it was tenofovir plasma levels or tenofovir  
5 diphosphate within the peripheral blood mononuclear  
6 cells, that relationship held up across men and  
7 women.

8           These studies shown here represent some of  
9 the larger studies conducted to date. But since  
10 Truvada for PrEP was approved seven years ago,  
11 there's an even larger data set that has  
12 accumulated.

13           Slide 1 up, please. The CDC recently  
14 updated their website with the new data on efficacy  
15 and analyses across all available data and  
16 concluded that adherence is highly correlated with  
17 outcomes for both men and women and that the  
18 efficacy of Truvada for PrEP is estimated to be 99  
19 percent for men and for women who are using Truvada  
20 for PrEP consistently.

21           DR. GOETZ: If I can follow up on that, then  
22 I guess my question goes into people who are

1 partially adherent. To the degree that it's  
2 knowable -- these are hard questions -- is partial  
3 adherence as effective in women as it is in men?  
4 This indirectly gets at the question, is partial  
5 adherence, we would think from the pharmacokinetic  
6 data would lead to similar concentrations of TFV  
7 diphosphate intracellularly and PBMCs, which may  
8 not be sufficient.

9 Does it protect women as well as men?  
10 Because if we get the same levels in PBMCs, they're  
11 at the lower level, so there may be concerns about  
12 tissue concentrations. So again, the question is,  
13 does partial adherence protect women as equally to  
14 men at thresholds? It's certainly going to be a  
15 relationship between adherence and success.

16 DR. DAS: There was some recent data  
17 presented just a few weeks ago at the IAS  
18 conference from the HPTN 082 study, which was a  
19 large study conducted in Africa in women. It was  
20 looking at different interventions to increase  
21 adherence. But in terms of the clinical outcomes  
22 of that trial -- put slide 3 up, please -- among

1 the 400 Women age 16 to 25, who were enrolled in  
2 this study, there were 4 infections. That gave an  
3 overall incidence rate of 1 per 100 person-years.

4 They used dried blood spots, which the  
5 methodology from the iPrEx study as well as from  
6 DISCOVER trial, and they found that the infections  
7 closely correlated with these measurements of  
8 adherence using the dried blood spots, which is to  
9 say that two of the infections occurred with no  
10 detectable drug level and the other two occurred in  
11 the setting of adherence consistent with less than  
12 2 doses per week. This is suggests that in the  
13 setting of low adherence, there is a similar  
14 relationship.

15 DR. BADEN: Dr. Giordano?

16 DR. GIORDANO: The adherence question  
17 relates to the PBMC question in my mind. The  
18 argument is that you achieve high levels of the  
19 tenofovir active component in PBMC, and that is a  
20 correlate of protection. My understanding of the  
21 Anderson et al data is that those data were  
22 generated from people who were less adherent to

1 people who were more adherent to the tenofovir  
2 drug.

3 So the PBMC data, are they not simply a  
4 measure of adherence? And if you measured  
5 tenofovir in hair or tenofovir in some other body  
6 component, would you not arrive at the same  
7 conclusion, that hair is a correlate of protection  
8 for HIV prevention? So it gets to the strength of  
9 those data, which are critical to this argument  
10 that the company's making.

11 DR. BRAINARD: So tenofovir diphosphate,  
12 when measured in red blood cells as is done with  
13 the dried blood spot analysis, is a measurement of  
14 adherence alone and can be analogous to measuring  
15 tenofovir in hair levels or measuring plasma  
16 tenofovir.

17 The advantage of the tenofovir diphosphate  
18 in dried blood cells is that it allows for an  
19 integrated assessment of efficacy over a longer  
20 period of time, similar to a hemoglobin A1c.  
21 Nevertheless, it doesn't speak itself to efficacy,  
22 but we know that for tenofovir prodrugs orally

1 administered, the drug is acting within CD-4  
2 positive T cells, which are a component of  
3 peripheral blood mononuclear cells.

4 We also can draw the correlation between the  
5 level of tenofovir diphosphate within the red blood  
6 cells and what the corresponding level is within  
7 PBMCs based on phase 1 studies in healthy  
8 volunteers that Dr. Anderson did to validate that  
9 analysis.

10 So the dried blood spot data is adherence  
11 data. You can get thresholds of adherence, and  
12 then based on the phase 1 studies done, where they  
13 were able to match those adherence bands to exactly  
14 how many doses were given per week, they can then  
15 correlate that to be expected intracellular PBMC  
16 levels, and we correlate that with efficacy because  
17 that's where we know that the virus replicates. It  
18 can only replicate in CD-4 cells

19 DR. GIORDANO: But that correlation with  
20 efficacy is still fundamentally based on adherence,  
21 as I understand it. How do we know that someone  
22 with the exact same adherence -- let me ask it

1 differently. How do we know that the levels in  
2 PBMC are the critical determinant of prevention,  
3 not of treatment efficacy for someone who has HIV,  
4 but of prevention? That's what I'm not -- you  
5 haven't really established that fact in my mind.

6 DR. BRAINARD: So we know that Truvada for  
7 PrEP is highly an equally effective in men and  
8 women and that adherence is the primary driver of  
9 that efficacy. When we look at the vaginal and  
10 rectal tissue levels of Truvada -- and I'll try to  
11 show you that slide in one minute -- what we can  
12 see is that the rectal levels of a tenofovir  
13 diphosphate following Truvada use are 100-fold  
14 higher than they are in vaginal tissue.

15 If genital tissue or rectal tissue -- and  
16 I'll put slide 1 up please. These are the data I  
17 just spoke to with the 100-fold higher rectal  
18 tenofovir diphosphate levels as compared to vaginal  
19 tenofovir diphosphate levels in the setting of  
20 Truvada with healthy female volunteers.

21 So if genital tissue levels were driving  
22 efficacy, then you wouldn't expect to see equal

1 efficacy in men and women. You'd see  
2 disproportionate efficacy, but we don't. We also  
3 know from the DISCOVER trial that Descovy is highly  
4 effective at preventing HIV acquisition in men who  
5 have sex with men and transgender women.

6 I'll put slide 2 up, please. These data add  
7 in the Descovy data in the vaginal and rectal  
8 compartments. What you can see is that for  
9 Descovy, rectal compared to vaginal, rectal levels  
10 are 10-fold higher. And within the rectal  
11 compartment, Truvada achieves 10-fold higher levels  
12 than Descovy.

13 So again, comparing Truvada to Descovy, if  
14 rectal levels were driving efficacy, then you would  
15 expect Truvada would be better than Descovy, but  
16 that's not what we saw in the trial. We saw that  
17 they were noninferior, and we saw that adherence  
18 was the primary driver of efficacy.

19 So we know that we have these high rectal  
20 levels. We know that vaginal levels with Truvada  
21 are lower, but we know that Truvada is highly  
22 effective in women who take the drug. Therefore,

1 that provides evidence, if you will, that the  
2 active tenofovir diphosphate and the circulating  
3 PBMCs is driving the efficacy and not the tissue  
4 levels within the homogenate of the tissue.

5 DR. BADEN: We have several more follow-on  
6 questions. Dr. Awni, did you have a follow on?

7 DR. AWNI: I actually thought it was a  
8 follow-on, but related to the size, there were a  
9 couple of statements saying the size of the two  
10 tablets between the Truvada and Descovy, how much  
11 difference in size? Size of the tablet could have  
12 an impact on somebody taking it, easy to take it  
13 somewhere else.

14 DR. BRAINARD: Yes. Descovy is  
15 substantially smaller than Truvada because it's  
16 such a smaller dose, 25 milligrams versus 300  
17 milligrams.

18 Slide 1 up, please. Obviously not to size,  
19 but you get the relative comparison between the  
20 size of the two pills there. And size has been  
21 cited in patient surveys as a factor that's been  
22 seen as favorable.

1 DR. BADEN: Dr. Gripshover, we're still  
2 doing follow-ons.

3 DR. GRIPSHOVER: My follow-on is back to the  
4 PBMC question. I think the data that we've seen,  
5 that you tried to show that it correlated with  
6 efficacy, was based on the iPrEx study of men who  
7 have sex with men, I think, and then we've seen it  
8 in the DISCOVER trial with Descovy.

9 Do we have data from Partners PrEP, where we  
10 did see Truvada being effective in women? Do we  
11 know that that also works in women from any other  
12 trials, or is it just in these two trials?

13 DR. BRAINARD: There are other trials  
14 besides Partners PrEP that showed efficacy in  
15 women. For example, TDF2 was a study conducted in  
16 both men and women, and in the TDF2 study, if you  
17 look at the as-treated population, which censors  
18 people after they have no longer been taking drug  
19 for at least 30 days, then the efficacy in men and  
20 in women is comparable.

21 DR. GRIPSHOVER: Actually, my question was  
22 do you have the T of the PMBC data in women in all

1 to know that that marker of efficacy works in those  
2 trials? That was my question; not did it work.  
3 Sorry.

4 DR. BRAINARD: So within Partners PrEP, we  
5 had adherence, but I don't believe that there were  
6 tenofovir diphosphate levels; it's plasma tenofovir  
7 levels. So we can take a look and see if we can  
8 find specific data regarding tenofovir diphosphate  
9 levels in clinical studies within women.

10 But what I would say, I want to reemphasize  
11 that the connection between adherence and the  
12 tenofovir diphosphate within PBMCs is made based on  
13 the validation of the dried blood spot assay. So  
14 you get the dried blood spot assay -- and I might  
15 have Dr. Anderson come up and speak to this just so  
16 he can walk through how that connection between the  
17 dried blood spot tenofovir diphosphate is then  
18 related and corresponding to a PBMC level.

19 Because it seems like what we're talking  
20 about is tenofovir diphosphate within the CD-4  
21 cells, within the PBMCs driving efficacy, but you  
22 don't actually measure the PBMCs during the study

1 for adherence; you measure the dried blood spot.  
2 Then we know from the validated assays what that  
3 level correlates to with respect to tenofovir  
4 diphosphate and PBMCs. I'll also say that we know  
5 across men, women, HIV infected, HIV uninfected,  
6 that tenofovir diphosphate levels are consistent.

7 DR. ANDERSON: Good morning. I have  
8 received grants and contracts from Gilead Sciences  
9 paid to my institution, as well as some consulting  
10 honoraria for my time here, but I do not have a  
11 financial interest in the outcome of this meeting  
12 or in the company.

13 So I wanted to explain the relationship  
14 between DBS concentrations in efficacy as well as  
15 PBMC concentrations and efficacy. If I can just  
16 have slide 2 up, please.

17 First, I want to start with DBS. DBS was  
18 used in the DISCOVER study as an adherence  
19 biomarker. What we measured is intracellular  
20 tenofovir diphosphate in red cells. And the reason  
21 is the half-life in the red cell is 17 to 20 days.  
22 That means the concentration will be proportional

1 to the exposure to the drug or adherence, so we'll  
2 have a proportional relationship there. It's a  
3 wonderful marker for assessing and quantifying  
4 adherence.

5 If I could have slide 3 up, please. The way  
6 that we operationalize this is dried blood spots  
7 come into the lab. We take a punch from that spot,  
8 so we normalize the amount that we assay. We then  
9 use a validated method. We get a result, the  
10 tenofovir diphosphate result. Then we have to  
11 understand what that result means.

12 To do that, we conducted separate directly  
13 observed dosing PK study in healthy volunteers, one  
14 Descovy and one with Truvada, and gave them varying  
15 adherence rates. Then we measured their  
16 concentrations. And we could tell by then the  
17 concentration, what adherence that person -- we  
18 made that a standard curve relationship.

19 Then we wanted to know do these bands of  
20 adherence relate with efficacy -- if I could have  
21 slide 2 up, please -- and they do. These are DBS  
22 results from the iPrEx open-label extension that

1 shows HIV incidence on the Y by the dried blood  
2 spot level on the X-axis. Then the different  
3 adherence bands you can see along the top, less  
4 than 2 doses per week on average, 2 to 3 and  
5 greater than 4.

6 People that had blood spot levels of greater  
7 than 4, there were no infections in that group.  
8 People who had blood spot levels of 2 to 3 had an  
9 approximately 90 percent reduction in HIV incidence  
10 relative to not being on PrEP. So if you hold  
11 those dosing categories in mind, this is very  
12 similar to what we see in PBMCs.

13 If I could have slide 2 up, please. Just  
14 switching your mind now from dried blood spots to  
15 PBMC intracellular tenofovir diphosphate, these are  
16 the active sites now in peripheral blood  
17 mononuclear cells. This is a case control from the  
18 iPrEx randomized-controlled trial, and the  
19 relationship between drug concentration in PBMC,  
20 tenofovir diphosphate in PBMC, and efficacy  
21 compared to placebo.

22 Now look at the bands along the top. These

1 are PBMC concentrations from a directly observed  
2 dosing study showing 2 doses per week on that as  
3 well as 4 or more doses per week. We saw  
4 approximately the same efficacy relationship in the  
5 PBMCs. Those that were in the roughly 2- to 3-dose  
6 range had about a 90 percent reduction. Those in  
7 the 4 or more had essentially a hundred percent  
8 reduction in HIV incidence.

9 That is the connection that we make through  
10 adherence. It's through adherence, and I think  
11 that was the point that was brought up earlier, is  
12 we're making a connection through adherence. The  
13 difference with PBMCs is we know that's the active  
14 site.

15 DR. BADEN: Dr. Swaminathan?

16 DR. SWAMINATHAN: So you've sort of drawn a  
17 line between --

18 DR. BADEN: Please talk closer to your  
19 microphone.

20 DR. SWAMINATHAN: You've sort of drawn a  
21 line between the levels from the dried blood spot  
22 test and PBMC levels, and the correlation with the

1 efficacy data. I guess the thesis is that because  
2 PBMCs or T cells are the sites of replication of  
3 the virus, and that TAF has good intracellular  
4 levels in PBMCs, that the efficacy would be  
5 expected to be as good or better.

6 But the connection between the PBMC levels  
7 in previous PrEP trials depends on the  
8 pharmacokinetics of Truvada. So whatever the  
9 actual target cell that's necessary for effective  
10 PrEP is, we know that it correlates with PBMC  
11 levels; not that the PBMCs are the actual target  
12 that makes PrEP efficacious.

13 How do we know that the correlation between  
14 the PBMC levels and cell X is the same with regard  
15 to the pharmacokinetics of these two different  
16 drugs?

17 DR. BRAINARD: So we know cell X. Cell x is  
18 a CD-4 positive T cell because that's the only cell  
19 within which HIV will replicate in order to spread  
20 infection. Now, that CD-4 positive T cell could be  
21 within the tissues or it could be within the  
22 peripheral blood mononuclear cells, recognizing

1 that these are not distinct subsets but that there  
2 is circulation around the body and trafficking of  
3 cells in and out of tissues.

4 I'll put slide 2 up, please, and then CC-15  
5 and back, please. Just reviewing, again, how  
6 infection is established, infection is initially  
7 established, for mucosal transmission, by the  
8 infection of a local cell. But in order for  
9 infection to disseminate, two different things need  
10 to happen. CD-4 T cells need to be recruited to  
11 that site of initial infection so that a founder  
12 population can be established, and then that  
13 founder population needs to disseminate via the  
14 lymphatic system.

15 We know from nonhuman primate studies that  
16 these CD-4 T cells that form the founder population  
17 are coming from the peripheral blood mononuclear  
18 cells, and we know that when you're talking about  
19 systemic oral drugs, that systemic drugs load both  
20 peripheral blood mononuclear cells, but there are  
21 also drugs circulating throughout the plasma.

22 Slide 2 up, please. Again, understanding

1       how that infection is occurring, with systemic  
2       therapy or with oral tenofovir prodrugs, drug is  
3       loaded within these peripheral blood mononuclear  
4       cells, which are circulating around the body and  
5       trafficking to different locations, including the  
6       lymphatic tissue, and including to tissue,  
7       particularly when there's a chemokinetic signal.  
8       But also TAF, in the case of Descovy and plasma  
9       tenofovir in the case of Truvada, are also  
10      circulating throughout the blood and distributing  
11      throughout the body. As those drugs get into the  
12      tissues, they're also able to load resident cells  
13      and provide protection that way.

14                So there are really two different ways that  
15      systemic oral agents can provide protection against  
16      HIV infection. Topical agents can also provide  
17      protection, but the way they do that is not by  
18      sitting on top of the mucosa but actually diffusing  
19      into the subepithelium [ph]. Then in the case of  
20      tenofovir gel, for example, they still have to get  
21      inside that CD-4 T cell because that's the only  
22      place that HIV replicates, and that's independent

1 of female, male, vagina, and rectum.

2 DR. SWAMINATHAN: I agree with most of what  
3 you said, but I would just have to disagree with  
4 this idea that there's this instantaneous dynamic  
5 flux in equilibrium between peripheral blood  
6 mononuclear cells and cervical or other submucosal  
7 lymphoid populations.

8 The phenotype of resident memory T cells in  
9 different tissues has been demonstrated to be  
10 different, and there are high CCR5 resident  
11 lymphocytes in vaginal tissue, for example, that  
12 are different from rectal tissue, and certainly  
13 different from PBMCs. Dendritic cells in the  
14 vaginal tissue are also thought to play a role.

15 All I'm saying is that unless one actually  
16 knows what the pharmacodynamics of these different  
17 compounds, intracellularly, in different resident  
18 populations, which is the population -- there's not  
19 recruitment until after the virus gets there, and  
20 there's infection locally of cells to come into the  
21 site of infection. So the level of intracellular  
22 drug in the lymphocytes that are going to be

1 infected immediately after exposure is what's  
2 relevant, and no one has really been able to  
3 measure, from what I understand.

4 DR. BRAINARD: I would like to -- oh, sorry.

5 DR. BADEN: Unfortunately, it's 11:07, and  
6 we need to go to the agency's presentation. I  
7 would have you respond, except this is a longer  
8 discussion. So I think, as I anticipated, we  
9 almost got through one question. So I will be very  
10 interested, as all the committee members are, on  
11 further discussion on this point. I think you  
12 understand the key issue, and perhaps over lunch,  
13 you'll further clarify how to educate us on the  
14 rationale.

15 But we need to move to the agency's  
16 presentation and clarifying questions to the  
17 agency. And if there's time, we'll come back to  
18 further clarifying questions to the applicant or  
19 we'll do that after lunch.

20 DR. BRAINARD: Great. Thanks very much.

21 DR. BADEN: Thank you.

22 Dr. Miele, thank you for presenting the

1 agency's perspective on some of these key issues.

2 **FDA Presentation - Peter Miele**

3 DR. MIELE: Good morning. I am Peter Miele,  
4 a medical officer in the Division of Antiviral  
5 Products. I will be presenting on behalf of the  
6 FDA review team for NDA 208215, supplement 12 for  
7 Descovy, for pre-exposure prophylaxis or PrEP  
8 indication. Here's my agenda.

9 I'll begin with a brief discussion of the  
10 indication being proposed by this application, and  
11 then move on to some context and background; in  
12 particular, a brief discussion of the issues we've  
13 been having here with regards to the potential role  
14 of mucosal tissue drug concentrations in HIV  
15 prevention.

16 I'll summarize the FDA findings from the  
17 DISCOVER trial in men and transgender women who  
18 have sex with men, and conclude with a discussion  
19 of the extrapolation approach that's being proposed  
20 in this application to support a PrEP indication in  
21 cisgender women and the data that has been  
22 submitted to support that approach.

1           As you know, this application proposes a new  
2           indication for Descovy or F/TAF, which is  
3           pre-exposure prophylaxis to reduce the risk of  
4           sexually-acquired HIV-1 in at-risk adults and  
5           adolescents weighing at least 35 kilograms.

6           To be clear, this indication would apply to  
7           adult and adolescent men and transgender women who  
8           have sex with men, men who have sex with women and  
9           cisgender women who have sex with men. As such,  
10          the proposed indication is similar to the currently  
11          approved indication for PrEP for Truvada, which is  
12          emtricitabine tenofovir disoproxil fumarate or  
13          F/TDF, and the indication is listed for you here.

14          Now, as you know, the data that the agency  
15          reviewed to support the PrEP indication for Truvada  
16          consisted of data from a phase 3 double-blind,  
17          placebo-controlled trial in MSM and transgender  
18          women, or the iPrEx trial; as well as phase 3,  
19          double-blind, placebo-controlled trial in adult  
20          heterosexual men and women in HIV serodiscordant  
21          relationships or the Partners PrEP trial; as well  
22          as data from a phase 2 open-label trial in

1 adolescent MSM. The Adolescent Trial Network study  
2 113.

3 As you've heard already, there are some  
4 differences between TAF and TDF. Both drugs have  
5 been approved for the treatment of HIV-1 and  
6 chronic hepatitis B, but compared to  
7 TDF 300 milligrams, oral administration of 25  
8 milligrams of TAF results in a 4- to 7-fold higher  
9 intracellular level of the active metabolite  
10 tenofovir diphosphate in PBMCs, while also  
11 resulting in 90 percent lower plasma levels of  
12 tenofovir.

13 It's these differences in the plasma  
14 exposure to tenofovir that may explain some of the  
15 differences in a safety profile observed between  
16 TAF and TDF, as if there's less circulating  
17 tenofovir in plasma, there's a reduction in the  
18 risk of off-target effects of tenofovir.

19 That said, there have been published  
20 single-dose PK studies that suggest that  
21 25 milligrams of oral TAF achieves lower tenofovir  
22 and tenofovir diphosphate levels in rectal and

1 vaginal mucosal tissues as measured in homogenates  
2 compared to oral 300 milligrams of TDF.

3           Why is this important? As you've heard in  
4 the previous discussions, the relative importance  
5 of mucosal tissue versus systemic drug  
6 concentrations to PrEP efficacy is unknown.  
7 Importantly, the minimum drug concentration in  
8 mucosal tissues, if they are relevant, that would  
9 be considered protective against HIV-1 infection is  
10 also unknown.

11           But we have some indirect observations that  
12 might support a role for mucosal tissue drug  
13 concentrations in PrEP efficacy. For one, as has  
14 been mentioned before, topical microbicide  
15 experience suggests that vaginal mucosal tissue,  
16 drug concentrations, at high enough levels and with  
17 very limited systemic exposure can reduce the risk  
18 of HIV-1 infection. And as you've heard, we know  
19 that oral TDF dosing results in lower tenofovir  
20 diphosphate exposure in vaginal tissue versus  
21 rectal tissue.

22           It is this differential drug distribution

1 that has raised concerns that in combination with  
2 poor adherence, it may have contributed to the  
3 mixed efficacy results observed in PrEP clinical  
4 trials of F/TDF in cisgender women as compared with  
5 MSM. That's a controversial topic, and that has  
6 been greatly debated over the last few years, but  
7 the end result is that we're not entirely sure to  
8 what extent this differential drug distribution may  
9 have on the efficacy; or in other words, is  
10 suboptimal adherence less forgiven in women than  
11 men?

12           These concerns have practical implications.  
13 The CDC PrEP guidelines, for example, acknowledge  
14 the lack of scientific consensus on protective  
15 contribution of drug exposure in specific body  
16 tissues. The CDC addresses this issue by reporting  
17 the time to achieve maximum intracellular  
18 concentrations of tenofovir diphosphate in the  
19 various compartments as based on PK studies. Some  
20 state PrEP guidelines have followed suit in  
21 recognizing the tissue differential also in  
22 discussing the time to achieve protective

1 concentrations.

2 For example, the New York State PrEP  
3 guidelines recommend a 7-day lead in of oral PrEP  
4 use for protection with receptive anal sex. In  
5 contrast, they recommend 20 days of daily PrEP use  
6 for protection with receptive vaginal sex. Now,  
7 these differences would not be necessary if there  
8 was consensus that systemic PK was the prime  
9 motivator or the prime driver for PrEP efficacy.  
10 As we know, there are no gender differences with  
11 respect to systemic PK for TDF.

12 So given that there is a lack of consensus  
13 regarding the contribution of local tissue versus  
14 systemic drug exposure to PrEP efficacy, and these  
15 reports of lowered mucosal tissue tenofovir  
16 diphosphate concentrations with oral TAF versus TDF  
17 dosing, the agency determined that fully powered  
18 clinical trials would be needed to support efficacy  
19 of F/TAF for PrEP using F/TDF as the active  
20 control.

21 Back to this application, the data that's  
22 been submitted to support a PrEP indication for

1 Descovy consists of one phase 3 double-blind active  
2 control clinical trial in MSM transgender women or  
3 the DISCOVER trial. To support indication in  
4 cisgender women and adolescents, an extrapolation  
5 approach has been proposed. The FDA presentation  
6 will focus on the extrapolation approach in  
7 cisgender women.

8 The DISCOVER trial was designed as a  
9 double-blind noninferiority trial of 5,000 subjects  
10 randomized to F/TAF or F/TDF for at least 96 weeks.  
11 Following the day 1 visits, subjects returned for  
12 study visits at weeks 4 and 12 and then every  
13 12 weeks. And at each follow-up visit, as you  
14 heard, they received at risk reduction counseling  
15 and adherence counseling, as well as STI screening  
16 at all three anatomical sites, oral, rectal, and  
17 urine.

18 The primary efficacy endpoint was the  
19 incidence of HIV-1 infections per 100 person-years  
20 when all subjects had reached a minimum of 48 weeks  
21 of follow-up and at least 50 percent had reached  
22 96 weeks of follow-up or permanently discontinued

1 from the trial.

2 For the relative risk analysis, a  
3 noninferiority margin of 1.62 per 100 person-years  
4 was derived based on historical data from three  
5 clinical trials of F/TDF for PrEP and MSM, namely  
6 the iPrEx, PROUD, and IPERGAY studies. Based on  
7 equal weighing of the three trials, an HIV  
8 incidence of 1.44 was assumed for the control arm  
9 of F/TDF with a confidence interval of 2.64 and  
10 9.7. Because the analysis for the DISCOVER trial  
11 was a rate ratio, the square root of the lower  
12 bound of this confidence interval provided the  
13 noninferiority margins. So the square root of 2.64  
14 is 1.62.

15 5,399 subjects were randomized in DISCOVER,  
16 6 subjects per arm were randomized but not treated,  
17 giving us a safety population of 5,387. The full  
18 analysis set was used for the primary efficacy  
19 analysis, and that consisted of subjects who were  
20 randomized and treated HIV negative at baseline and  
21 had at least one follow-up HIV test during the  
22 trial, and that population was 5,335.

1           In the safety population, the baseline  
2 characteristics and demographics were well balanced  
3 between the two arms. As you've heard, the median  
4 age was 34 years, and 99 percent of subjects were  
5 MSM and 1 percent were transgender women; 84  
6 percent of subjects were white, black, or mixed  
7 black race made up 9 percent of subjects and  
8 Hispanics made up 25 percent.

9           At baseline, 16 percent of subjects were  
10 using Truvada for PrEP and 44 percent were  
11 uncircumcised. The median duration of exposure was  
12 86 weeks, and that was balanced between the two  
13 arms. And as you've heard, adherence to study drug  
14 was high by multiple measures in this trial.

15           For the primary efficacy analysis, a total  
16 of 22 HIV infections were reported, 7 in the F/TAF  
17 arm for an HIV infection rate of 0.16, and 15 in  
18 the F/TDF arm for an HIV infection rate of 0.342.  
19 The HIV infection rate ratio was 0.468 with the  
20 confidence intervals shown here. Because the upper  
21 bound of the confidence interval was below the  
22 prespecified NI margin of 1.62, the DISCOVER trial

1 demonstrated noninferiority of F/TAF to F/TDF.

2 As an update, we received a report of an  
3 additional HIV infection after the submission was  
4 filed, one more HIV infection in the F/TAF group,  
5 but this does not impact the primary efficacy  
6 conclusion.

7 Data from the DISCOVER indicate that F/TAF  
8 provides a similar level of protection as F/TDF  
9 against rectal acquisition of HIV, but if we  
10 consider other potential routes of HIV transmission  
11 in men, such as penile HIV exposure, we do not have  
12 any direct evidence to support the efficacy of  
13 F/TAF for this relatively low-risk route of  
14 transmission.

15 That said, we can assume that insertive sex  
16 was occurring in the DISCOVER trial. At study  
17 entry, subjects reported a mean of 4 unprotective  
18 insertive anal intercourse partners in the 90 days  
19 prior to screening, and during the trial, 16  
20 percent of subjects had urethritis diagnosed with  
21 gonorrhea or chlamydia likely from unprotected  
22 insertive anal intercourse.

1           Thus, given the low rates of HIV infection  
2 observed overall in the DISCOVER trial, it may be  
3 reasonable to assume that men who practice  
4 insertive sex were protected.

5           I'm now going to switch gears and talk about  
6 safety as observed in the DISCOVER trial. Both  
7 F/TAF and F/TDF were safe and well tolerated. We  
8 observed no notable differences between the two  
9 arms in the types, incidence, severity, or onset of  
10 adverse events, or laboratory abnormalities.

11           As you've heard, the most common AEs were  
12 sexually transmitted infections. If we exclude the  
13 STIs and other infectious adverse events, the most  
14 common AEs were diarrhea at 16 percent, nausea at 7  
15 percent, headache at 7 percent, and fatigue at 6  
16 percent, with comparable rates between the arms.

17           Six percent of subjects in the F/TAF arm  
18 were considered serious adverse events and 5  
19 percent of subjects in the F/TDF arm had serious  
20 adverse events. The majority of these events were  
21 not considered related to study drug. We also  
22 observed low rates of adverse events leading to

1 drug discontinuation, 1 percent in the F/TAF arm  
2 and 2 percent in the F/TDF arm.

3 The most common adverse events leading to  
4 drug discontinuation were gastrointestinal  
5 disorders, which led to drug withdrawal in less  
6 than 1 percent of subjects in each arm. When we  
7 looked at GI events overall, they tended to occur  
8 in the first month of treatment, which is  
9 consistent with the start-up syndrome described in  
10 previous trials of F/TDF PrEP.

11 These issues did not seem to have a major  
12 impact on body weight, however, there was a mean  
13 increase of weight from baseline at week 48 of  
14 1.1 kilograms for F/TAF and essentially no change  
15 in weight for F/TDF.

16 Looking at renal safety, when we looked at  
17 the mean absolute change in serum creatinine, there  
18 was minimal change in either group at both weeks 48  
19 or 96. The graph on the right shows the mean  
20 change in estimated GFR from baseline. The blue  
21 line shows the changes in the F/TAF group, which  
22 essentially stayed pretty much consistent with

1 baseline, whereas in the F/TDF group, there was a 2  
2 to 5 milliliter per minute decrease from baseline  
3 over the course of the trial, which became apparent  
4 as early as week 4.

5 The distribution of urine protein to  
6 creatinine ratio, or UPCR categories, was a key  
7 alpha protected safety endpoint in this study.  
8 UPCR is generally regarded by the FDA Division of  
9 Cardiovascular and Renal Products as a useful  
10 laboratory assessment of proteinuria.

11 As shown here, the proportion of subjects  
12 who had no significant proteinuria at baseline and  
13 who then went on to develop significant proteinuria  
14 at week 48 was low in both groups, but was higher  
15 in the F/TDF group at 2 percent versus 1 percent in  
16 the F/TAF group.

17 Conversely, the proportion of subjects who  
18 had significant proteinuria at baseline, of which  
19 there were only 25 per arm and who then had  
20 improvement in their UPCR category, was higher in  
21 the F/TAF group compared to the F/TDF group, at 57  
22 versus 44 percent, respectively. These differences

1 were statistically significant at week 48, however,  
2 the differences were not significant at week 96.

3 We also observed a greater frequency of  
4 treatment emergent proteinuria by urine dipstick in  
5 the F/TDF arm overall at 24 percent versus 21  
6 percent per F/TAF. Most of these abnormalities,  
7 however, were grade 1, and we saw no difference in  
8 the frequency of grade 2 proteinuria between the  
9 two arms.

10 Likewise, we saw very little differences in  
11 the frequencies of graded treatment-emergent  
12 laboratory abnormalities as they pertained to serum  
13 creatinine, 2 percent for F/TDF and 1 percent for  
14 F/TAF overall, and we saw no differences at all  
15 between the two groups with respect to  
16 hypophosphatemia regardless of severity.

17 Likewise, we saw very little difference  
18 between the two groups in the frequency of  
19 treatment-emergent adverse events related to renal  
20 safety. There was one case of Fanconi syndrome  
21 acquired in the F/TDF arm, but also a case of  
22 glomerulonephropathy in the F/TAF arm, as well as a

1 case of nephrotic syndrome in the F/TAF arm.

2 The cases in the F/TAF were not considered  
3 related to study drug, whereas the Fanconi syndrome  
4 in the F/TDF arm was. But when we looked at other  
5 adverse events as grouped by their MedDRA high  
6 level terms for renal failure and impairment,  
7 urinary abnormalities, electrolyte analyses, namely  
8 blood phosphorous, decreased renal function, and  
9 urinalysis not elsewhere classified, we saw no  
10 differences between the groups in the reporting of  
11 these adverse events. Likewise, there was very  
12 little difference between the two groups in renal  
13 adverse events that led to drug discontinuation,  
14 although the numbers were very small.

15 In summary, for adverse events or graded  
16 treatment-emergent laboratory abnormalities related  
17 to renal function or safety, we observed no major  
18 differences between the two groups in this  
19 particular subject population. I would also remind  
20 you that, as with Truvada, approved labeling for  
21 Descovy still carries with it a warning for new  
22 onset or worsening renal impairment.

1           Moving on to bone safety, mean percent  
2 change from baseline at week 48 and hip and spine  
3 bone mineral density were also key alpha-protected  
4 safety endpoints. As shown on the table here,  
5 there were differences between the two groups at  
6 both hip and spine and at both weeks 48 and 96,  
7 with essentially no great change in the F/TAF arm  
8 but decreases of about a mean of 1 percent at each  
9 time point, at each site for the F/TDF arm. These  
10 differences were statistically significant at both  
11 time points.

12           Consistent with other tenofovir-containing  
13 product labeling, we conducted a categorical  
14 analysis of the percent change in BMD from baseline  
15 using the falling cutoffs, 7 percent change from  
16 baseline for hip and 5 percent change from baseline  
17 for spine, as these are cutoffs that the agency  
18 considers clinically meaningful.

19           With regards to the hip, we saw absolutely  
20 no difference between the two arms, whether in  
21 decreases or increases. We also saw no difference  
22 between F/TAF and F/TDF for decreases from baseline

1 in spinal BMD. However, there was a slight or  
2 greater proportion of subjects in the F/TAF arm  
3 that had a 5 percent or greater increase from  
4 baseline in spine BMD at week 48.

5 The applicant has shown you results from a  
6 categorical analysis regarding the change in BMD  
7 clinical status from baseline to week 48 for the  
8 spine. We concur that there was a greater  
9 proportion of subjects in the F/TDF arm that had  
10 worsening status at week 48 and conversely a  
11 greater proportion of subjects in the F/TAF arm  
12 that had greater improvement of their BMD status in  
13 the hip at week 48.

14 However, when we did the same analysis for  
15 the hip, we saw no differences in the proportion of  
16 subjects at worsening status at week 48, and there  
17 was actually a greater proportion of subjects in  
18 the F/TDF arm that had improvement.

19 When we turn to adverse events as reported  
20 in the DISCOVER trial, during the course of the  
21 trial, we saw no differences between the two groups  
22 with respect to fractures, most of which were

1 traumatic and occurred at a relatively low rate of  
2 2 percent, or in pathological fractures, as well as  
3 in reports of back pain, spinal pain, or bone pain.  
4 Likewise, we saw no differences between the two  
5 groups with respect to what the investigators  
6 themselves reported as bone density decrease, bone  
7 loss, osteopenia, osteoporosis, or  
8 hypophosphatemia.

9 We looked also at the median change from  
10 baseline in fasting serum lipids, and we noticed  
11 that there was an overall trend to decrease in  
12 fasting cholesterol and LDL in both arms, but the  
13 magnitude of the decrease from baseline was greater  
14 for F/TDF. We also noted that there was a slight  
15 increase from baseline in fasting triglycerides  
16 with F/TAF.

17 However, it's important to note that we saw  
18 no differences in the median change from baseline  
19 for the ratio of total cholesterol to HDL, either  
20 within groups or between groups. That said, the  
21 F/TAF group had consistently higher incidence of  
22 graded laboratory abnormalities related to total

1 cholesterol, LDL, or triglycerides, across all  
2 toxicity levels.

3           Lastly, we conducted a categorical analysis  
4 of the shifts from baseline based on LDL categories  
5 as adapted from the NIH's National Cholesterol  
6 Education program. As shown here, we found that a  
7 greater proportion of subjects in the F/TAF group  
8 had worsening LDL category at week 48 compared to  
9 the F/TDF group, 17 versus 10 percent. And  
10 conversely, a greater proportion of subjects in the  
11 F/TDF group had improvement in the LDL category  
12 compared to F/TAF, 40 versus 28 percent,  
13 respectively.

14           These findings did not translate into any  
15 major differences between the two groups with  
16 respect to adverse events, clinical adverse events,  
17 such as the cerebrovascular or cardiovascular  
18 events, which were very low in the trial anyway.  
19 That said, while the proportion of subjects who  
20 were on lipid-modifying agents at study entry was  
21 balanced between the two arms, a slightly greater  
22 proportion of subjects in the F/TAF arm initiated

1 these agents during the study at 2 percent versus  
2 1 percent for the F/TDF arm.

3 In summary, again, both F/TAF and F/TDF were  
4 both safe and well tolerated. Differences between  
5 the groups were observed for various indices,  
6 namely changes from baseline in renal biomarkers,  
7 bone mineral density on DEXA scans, and fasting  
8 serum lipids, consistent with previous trials that  
9 compare TAF to TDF. In general, F/TAF and F/TDF  
10 had similar adverse event profiles, including low  
11 rates of serious adverse events or adverse events  
12 leading to drug discontinuation.

13 I'll now turn to our discussion of the  
14 indication for PrEP in cisgender women, but before  
15 that, we acknowledged that conducting a trial in  
16 women for a PrEP indication is challenging. As you  
17 know, previous clinical trials in women have  
18 demonstrated variable efficacy of oral F/TDF,  
19 mostly driven by adherence it seems. As such, FDA  
20 recommends superior designs whenever possible for  
21 trials in women because determination of a  
22 noninferiority margin is not readily feasible.

1           In this application, two extrapolation  
2 strategies are proposed. One is the extrapolation  
3 of F/TAF efficacy from MSM in the DISCOVER trial to  
4 support indication in cisgender women. For this,  
5 one must demonstrate comparable systemic exposures  
6 between men and cisgender women, including  
7 tenofovir and TAF concentrations in plasma, as well  
8 as tenofovir diphosphate concentrations in the  
9 PBMCs.

10           The second approach is to extrapolate  
11 efficacy from F/TDF to support F/TAF in women. And  
12 as you've heard, this approach makes use of a  
13 published EC<sub>90</sub> value of 40 femtomole per million  
14 PBMCs as derived from the iPrEx trial of F/TDF in  
15 MSM. For this approach, one must demonstrate  
16 comparable or higher tenofovir diphosphate  
17 concentrations in systemic PK but also in cervical  
18 vaginal tissue with TAF relative to TDF.

19           With respect to the first approach, we don't  
20 expect that there's going to be any clinically  
21 relevant differences in the PK of emtricitabine, or  
22 TAF, or PBMC-associated tenofovir diphosphate

1 between men and women. However, for reasons that  
2 have been discussed already, matching systemic drug  
3 exposures alone may not suffice because of the  
4 unknown contribution of mucosal tissue  
5 concentrations to PrEP efficacy.

6 For the second approach, where we tried to  
7 extrapolate efficacy of F/TDF to support F/TAF,  
8 while there's some overlap with the prior approach  
9 regarding systemic drug exposures, for this  
10 approach, the applicant has cited 40 femtomole of  
11 tenofovir diphosphate per million PBMCs as a  
12 threshold, or EC<sub>90</sub> value, for PrEP efficacy.

13 The two things to consider here, as you've  
14 heard, this threshold concentration was associated  
15 with adherence to 3 to 4 doses of F/TDF per week,  
16 specifically in MSM from the iPrEx trial. Also,  
17 this concentration has not been validated as a PK  
18 surrogate for tenofovir-based PrEP efficacy for all  
19 populations.

20 The concern with relying on this PBMC  
21 threshold concentration is that it may not  
22 accurately reflect the drug concentrations at the

1 tissue level. For example, we know that with  
2 F/TDF, with multiple dosing, we can achieve this  
3 threshold concentration of 40 femtomoles per  
4 million PBMCs in a matter of days, about 3 days.  
5 And we know that this concentration in PBMCs  
6 correlates to a rectal tissue concentration that is  
7 greater than the 100 femtomoles per milligram or  
8 significantly greater than the lower limit of  
9 quantification.

10 In contrast, a single dose of F/TAF can  
11 reach this PBMC concentration of 40 femtomoles in a  
12 matter of hours, but the vaginal tissue  
13 concentration can be reported as below the level of  
14 quantification. In both scenarios, we have  
15 achieved this threshold concentration that's being  
16 proposed as a surrogate in PBMCs with diverse  
17 results in relevant tissue concentrations.

18 The more conservative approach is to try to  
19 match PK, both systemic and tissue, to support an  
20 extrapolation of F/TDF efficacy in cisgender women  
21 to F/TAF in the same population. For the systemic  
22 part of this extrapolation approach, we already

1 know that TAF achieves higher levels of tenofovir  
2 diphosphate in PBMCs, so we can check that off.

3 With regards to the tissue concentrations,  
4 we know that single-dose TAF or TDF results in  
5 concentrations that are mostly below the level of  
6 quantification in tissue. What we don't know is  
7 whether multiple dosing with TAF or TDF achieves  
8 different results at the tissue level. And to that  
9 end, data from an external study in healthy female  
10 volunteers, study A15-137, was submitted to support  
11 this latter part of the extrapolation.

12 This is the study design for study A15-137.  
13 It was conducted in two parts, including a single  
14 dose and multiple dose part where subjects were  
15 treated for 14 days with F/TAF or F/TDF. We're  
16 going to focus only on the approved doses for F/TAF  
17 and F/TDF.

18 Multiple samples were collected for PK and  
19 plasma, PBMC, rectal and cervical vaginal fluid, as  
20 well as tissue biopsies, and we're going to focus  
21 on the results for the rectal cervical and vaginal  
22 tissue biopsies here, and in particular the

1 evaluations for tenofovir diphosphate  
2 concentrations.

3 I will also note one thing about this  
4 particular study design is that each woman  
5 contributed cervical vaginal tissue samples at only  
6 one given time point, and that's because tissue  
7 samples were collected at different clinical sites  
8 at different time points. Rectal tissues were  
9 collected 4 hours post dose following 14-day  
10 administration. Cervical vaginal tissues were  
11 collected at 4 hours post-dose following  
12 single-dose administration, as well as 4, 24, and  
13 48 hours following 14-day administration.

14 The measurement in this study were tissue  
15 homogenates, and assuming a tissue density of  
16 1 gram per mL, final sample concentrations in the  
17 lower limit of quantitation of 0.3 nanograms per mL  
18 were converted to fmol/grams for tenofovir  
19 diphosphate.

20 Here are the results that we obtained.  
21 Following single-dose administration of F/TAF or  
22 F/TDF, 83 percent of vaginal tissue samples were

1 below the lower limit of quantitation, or BLQ, at 4  
2 hours. Following multiple doses of F/TAF or F/TDF,  
3 a significant proportion of tissue PK samples were  
4 also BLQ.

5 In vaginal tissues, tenofovir diphosphate  
6 concentrations were higher for oral F/TAF dosing  
7 compared to F/TDF only at 4 hours post-dose, but  
8 they were mostly unquantifiable at 24 and 48 hours.  
9 It is unclear if this isolated finding at 4 hours  
10 translates to comparable or higher tenofovir  
11 diphosphate concentrations in vaginal tissues  
12 beyond 4 hours after multiple dose administration.

13 This table represents the results from the  
14 multiple dose part of the study. It's a busy  
15 study, so I'll try to walk you through it. If you  
16 look at the first row, the 4-hour row and at the  
17 column for F/TDF, you'll see that 62 percent of  
18 vaginal tissue samples in the F/TDF arm were below  
19 the level of quantification. In contrast, none of  
20 the tissues in the F/TAF arm were BLQ.

21 Correspondingly, a median tenofovir diphosphate  
22 concentration was calculated at 151 femtomoles per

1 milligram.

2           Similar results were seen with cervical  
3 tissue biopsies, and as for the rectal tissue, the  
4 results confirmed the previous reports that dosing  
5 with oral F/TDF results in higher tenofovir  
6 diphosphate concentrations in rectal tissue  
7 compared to F/TAF dosing.

8           However, for 24 hours and 48 hours, the  
9 majority of the tissue samples for the vaginal and  
10 cervical tissues were below the level of  
11 quantification, and we were not able to determine a  
12 median tenofovir diphosphate level for these  
13 tissues with any degree of confidence.

14           In conclusion, F/TAF and F/TDF afford  
15 similar protection against sexual acquisition of  
16 HIV-1 infection in MSM and transgender women at  
17 substantial risk. Both F/TAF and F/TDF are safe  
18 and well tolerated. F/TAF dosing results in  
19 smaller changes or improvements from baseline in  
20 biomarkers of proteinuria and bone mineral density  
21 compared to F/TDF, but with less favorable lipid  
22 changes. No major differences were noted with

1 respect to the side effect profile during the  
2 course of this study.

3           However, clinical data regarding the use of  
4 F/TAF for PrEP in cisgender women are lacking.  
5 Robust tenofovir diphosphate concentration data in  
6 the female genital tract are lacking. This  
7 application proposes a PrEP indication in cisgender  
8 women based on extrapolation of efficacy data via  
9 tenofovir diphosphate concentrations and peripheral  
10 blood mononuclear cells. However, the relative  
11 importance of mucosal tissue versus systemic drug  
12 concentrations to PrEP efficacy remains unknown.

13           That concludes my presentation, and I'll  
14 take any clarifying questions from the committee.

15                           **Clarifying Questions**

16           DR. BADEN: Thank you.

17           We will now take clarifying questions for  
18 the agency's presentation, and I think  
19 Dr. Daskalakis has the first question.

20           DR. DASKALAKIS: Peter, thanks for that  
21 presentation. Just a question that may also  
22 overlap with a question to the sponsor. You state

1 that there's evidence that TAF/FTC is effective in  
2 preventing HIV in MSM and transgender women, but  
3 we've never actually seen the transgender female  
4 data broken out in any way.

5 Do you have a sense of what that really  
6 looks like or is that a better question to defer to  
7 the sponsor?

8 DR. MIELE: What I can say, and the  
9 applicant is free to chime in, first, there was a  
10 very small proportion of transgender women  
11 enrolled. I believe about 30 percent dropped out  
12 early during the course of the trial. None of the  
13 HIV infections were seen in the transgender women.  
14 Beyond that, I can't really say too much.

15 DR. DASKALAKIS: And a related question, any  
16 pharmacokinetic data on tenofovir and TAF versus  
17 TDF, versus Truvada, in regards to whether any of  
18 those transwomen were using estrogen?

19 DR. MIELE: I will defer to the applicant as  
20 to concomitant medications being used by the  
21 transgender women in the study. We have seen  
22 reports about the effect of PrEP with feminizing

1 hormone therapy, TAF, but no clinical drug  
2 interaction studies have been conducted with TAF  
3 and feminizing regimens.

4 I don't know if our clinical pharmacology  
5 reviewer would like to discuss this topic further.

6 DR. ZHENG: Yes. There's no clinical drug  
7 interaction study that's being conducted with TAF  
8 and feminizing regimens, CYP-based drug  
9 interactions are likely to be minimal. However,  
10 some studies suggest that the estrogen can change  
11 phosphorylation and the phosphorylation of  
12 leukocytes and their analogs.

13 The study conducted with TDF in transgender  
14 women receiving feminizing regimens, the paper  
15 published recently by Dr. Cottrell, showing minimum  
16 changes in plasma tenofovir concentrations for the  
17 transgender woman and minimal changes in tenofovir  
18 diphosphate concentration in PBMC for rectal tissue  
19 as well.

20 The similar dATP to cisgender men, there was  
21 significantly higher dATP in rectal tissues as  
22 compared to ciswomen. We know that dATP may lower

1 effective concentration of tenofovir diphosphate in  
2 rectal tissues. The sample size is very small, so  
3 it seems like the study shows that the lower  
4 concentration of tenofovir diphosphate is mostly  
5 driven by the higher dATP levels in rectal tissue,  
6 but we don't have any data for TAF. I don't know  
7 if the sponsor has more to add.

8 DR. BADEN: One second, Dr. Daskalakis. I  
9 would ask the applicant -- this is clarifying  
10 questions to the agency. We realize the applicant  
11 has important data in that space. So if you can  
12 keep a list of these questions, then we will come  
13 back and engage your data set after we clarify with  
14 the agency.

15 Do you have further --

16 DR. DASKALAKIS: I'll hold for that.

17 DR. BADEN: No other follow-on. Then,  
18 Dr. Green?

19 DR. GREEN: This is not a follow-on.

20 DR. BADEN: Correct.

21 DR. GREEN: Thank you. If we could see your  
22 slide 46 again. I just want to make sure I

1 understand it. It was I think the last slide you  
2 gave in your presentation, the one that you  
3 described as complicated.

4 Now, my question is, simplistically for  
5 percent BLQ, you want it to be lower because that's  
6 the percentage, below the level that's quantified.  
7 It's not really telling us what level is present;  
8 it's just whether anything can be quantified or  
9 not. And if I'm looking at this correctly -- I  
10 just want to make sure I'm reading this  
11 correctly -- I see that at 4 hours that F/TAF in  
12 the vagina appears to be better than F/TDF, and in  
13 cervical tissue, it appears to be better.

14 Then at 24 hours, F/TAF is not as good, but  
15 neither one of them are very good in both  
16 vaginal -- and it flips because it's better in  
17 cervical, but neither one's very good. And at  
18 48 hours, basically they all are not good. But  
19 we're also demonstrating here that F/TDF doesn't  
20 have that level of protection over time either.

21 So if mucosal levels are important, this  
22 slide does not demonstrate that because you're not

1 seeing a difference that benefits F/TDF, which  
2 already has a drug indication and has been shown to  
3 be efficacious. Is that correct?

4 DR. MIELE: I don't know that we can say  
5 that one is better than the other. The tissue  
6 samples are just not quantifiable, so we can't  
7 really say much of anything about that. But I  
8 agree with you that the TDF samples were also not  
9 showing much. And it may be an issue with the  
10 assay. It may be the cutoffs that we used to  
11 determine quantifiable.

12 Again, I don't know if the clin/pharm  
13 reviewer has any other input here.

14 DR. ZHENG: Backup slide with the LLQ  
15 question.

16 DR. HOTAKI: Can you tell me which number it  
17 is?

18 DR. ZHENG: Slide 79. Oh, no, slide 80.

19 You can see the published study used  
20 compatible units for the lower limit of  
21 quantitations, and some are using a femtomole  
22 sample or nanogram per mL, which makes it difficult

1 to compare assays sensitivities across studies.

2 In this, A15-137, we have a higher LLQ  
3 compared to other study reported. The difference  
4 in LLQ can be due to tissue biopsy size, and  
5 because it's converted from the nanogram per mL to  
6 femtomole per gram, so you have a smaller sample  
7 size, it's more possible to have the LLQ values.

8 Also related to the sample storages,  
9 stability, and some of those studies may not have  
10 the long-term stability data, and also recovery  
11 efficiencies, and also the assay sensitivity. So  
12 it's probably related to, also, the assay  
13 sensitivity, also has other issues.

14 DR. BADEN: Dr. Siberry, a follow-on?

15 DR. SIBERRY: Thanks very much. In thinking  
16 about this problem of understanding whether the  
17 drug levels in the genital compartment are the  
18 actual proxy for protection, have you looked at the  
19 trials where the only difference in treatment was  
20 TAF and TDF in women to see if there was any  
21 difference in plasma genital discordance and  
22 suppression?

1           We know that some women who are on  
2 suppressive therapy still can have HIV present in  
3 the genital tract, and that may be an additional  
4 way to get at a differential impact of TAF versus  
5 TDF in the genital compartment.

6           Then just a follow-on, can you comment from  
7 the agency perspective about how we should view the  
8 appropriateness of an application for a drug that  
9 intended all the while to have an indication in men  
10 and women, coming in with clinical trial data only  
11 for men with an expectation to apply to women? I'm  
12 just concerned because often women are excluded  
13 because of concerns about fetal safety and possible  
14 pregnancy and other reasons, and this feels to me  
15 like a potentially concerning precedent. Thanks.

16           DR. MIELE: To your first question, we have  
17 not looked at that data. You're talking about an  
18 HIV treatment. We have not looked at that data, at  
19 least I'm not aware if the company has that  
20 information, but we have not.

21           Second question, ideally, the agency would  
22 like to see clinical trials in the populations for

1 which labeling is going to be indicated. We  
2 recognize that conducting trials in women in the  
3 current landscape with Truvada approved is  
4 challenging. I think our first initial hurdle was  
5 to agree on a trial, period; and that ultimately  
6 was decided to be conducted in MSM and transgender  
7 women.

8           Discussions about a trial in women were had  
9 with the applicant. And again, we noticed that  
10 there were challenges and difficulties, and the  
11 agency itself was struggling with the appropriate  
12 study design to recommend for this population. But  
13 it was never really agreed upon that this  
14 particular application, the way it appeared, would  
15 support the indications that are being requested.

16           So at this point we're trying to work with  
17 what was submitted to see if we can justify an  
18 indication across the populations based on a study  
19 that was conducted in one particular population.  
20 But going forward, no; we're were not recommending  
21 this particular approach. And again, as Dr. Murray  
22 noted, this particular case is unique because we're

1 talking about basically two prodrugs or the same  
2 drug, and we have an approved drug already for  
3 Truvada in all those populations. But ordinarily  
4 we would not rely on a single trial in one  
5 population to support an indication across multiple  
6 populations.

7 DR. BADEN: Dr. Siberry got two questions in  
8 there, and I have two follow-ons, one for each of  
9 his questions.

10 Given your review of the sum total of the  
11 data, what is your impression, or the agency's  
12 impression, of a marker of protection in the  
13 vaginal compartment? Has that emerged or is that  
14 still unclear given the state of the data?

15 DR. MIELE: I think that remains very much  
16 unclear. I also want to emphasize that it's not a  
17 one or other. It's not necessarily mucosal tissue  
18 versus systemic. There may be a contribution of  
19 both going on here, and that's the part we don't  
20 understand.

21 If vaginal tissue concentrations are  
22 relevant, are they acting as the primary line of

1 defense, and is systemic acting as a backup? I  
2 think that was a theory that was floated by  
3 Dr. Anderson actually. But we don't know at this  
4 point. The only thing we can measure are these  
5 tissue homogenates. Some studies have looked at  
6 mononuclear cells within the vaginal tissues  
7 themselves and have had mixed results with respect  
8 to differences with the vaginal compartment and the  
9 rectal compartment. I think the field itself, at  
10 least to us, is a bit mixed or conflicted. So that  
11 first question you asked is very much unclear in my  
12 opinion.

13 DR. BADEN: Part of the challenge -- and  
14 other members of the committee have mentioned this,  
15 and I'll ask this of the applicant as well  
16 later -- the vaginal compartment, there are  
17 menstrual cycle issues, microbiome issues,  
18 behavioral issues that are different than other  
19 compartments, and it may be adherence or PBMC  
20 concentration that may be all that matters, or  
21 there may be an interaction with these other  
22 factors.

1           Trying to understand from the data available  
2 to determine if perhaps adherence is all we need,  
3 which is in part what's being suggested, still I am  
4 struck by VOICE and the other trials that did not  
5 show even results in protection, although there are  
6 explanations. It always worries me when there are  
7 lots of explanations and were asked to embrace the  
8 positive but not worry about the negative, and then  
9 assume that it should just work the way we want it  
10 to.

11           So I guess my question is, should we just  
12 assume the vaginal compartment is an extension of  
13 the systemic component, in this setting? And  
14 obviously, this will be asked of the applicant  
15 later, which is building on the conversation we've  
16 been having for an hour or two.

17           DR. MIELE: I think it would be challenging  
18 to do that given that we know that the  
19 pharmacokinetics are very different between TAF and  
20 TDF, and I think part of that difference that we  
21 see systemically may be extending to the  
22 compartments in question, for various reasons. TDF

1       itself may be cycling in the GI tract and achieve a  
2       high protection in the rectal tissue, for example.  
3       I don't know that we can confidently say that we  
4       can extend the systemic to tell us what's going on  
5       in the vaginal tissue.

6               DR. BADEN: My other follow-on I will take  
7       in a minute. I will continue to follow on, on this  
8       line of questioning.

9               Dr. Ofotokun?

10              DR. OFOTOKUN: Kind of along this line of  
11       discussion was the significance of the time for  
12       achieving protective concentration. That was  
13       different for TDF, for different populations. It  
14       was different for men and also different for women  
15       from what we saw. And I think the guidelines vary  
16       from state and different regions of the country  
17       based on this time to achieve a protective  
18       concentration for TDF.

19              Do we have a sense of that variability with  
20       TAF?

21              DR. MIELE: I'll say this. I think the  
22       guidelines are being conservative because of this

1       uncertainty around the role of tissue  
2       concentration. I think CDC has presented the data  
3       for prescribers to be aware of, and then some state  
4       guidelines have pushed that even further into  
5       actual prescribing recommendations.

6                Again, I think in the services trying to be  
7       the most conservative, for TAF, we don't have any  
8       information like that. It really depends on  
9       whether you believe that systemic PK is the driver  
10      of protection, in which case you probably don't  
11      need this lead-in time. But if you believe at all  
12      that tissue may be contributing to PrEP efficacy, I  
13      don't think we have any data to even help us with  
14      what's going on with TAF, at least in the vaginal  
15      tissue.

16               DR. BADEN: Dr. Swaminathan?

17               DR. SWAMINATHAN: These are drugs that stop  
18      viral replication; they're not disinfectants. So  
19      the applicant's very valid points that it's T cells  
20      that are the issue, is it really useful to look at  
21      drug concentrations of homogenates of biopsies,  
22      which are primarily everything but lymphocytes?

1 DR. MIELE: Well, in retrospect, probably  
2 not. Going into this, what we had were these  
3 single reports out there that were surprising I  
4 think to the community that TAF was acting so  
5 differently in local tissue compartments. And it's  
6 probably what drove us to be conservative and  
7 request a clinical trial to begin with.

8 If it had been established that systemic PK  
9 were the main driver, we probably didn't need the  
10 DISCOVER trial and 5,000 men. But there was a fair  
11 amount of uncertainty, as I've tried to describe to  
12 you, both in the literature and in the guidelines,  
13 so the trial was conducted.

14 Now, I will say this. Granted, rectal  
15 tissue concentrations with TAF are lower compared  
16 to TDF, and the DISCOVER trial shows comparable  
17 efficacy results regardless, but we don't know what  
18 the minimum concentration would be. It may be that  
19 whatever concentration is being achieved with TAF  
20 and rectal tissue may suffice; we don't know.

21 But you're right. I don't know that tissue  
22 homogenates is really the best measure to give us

1 valuable information at this point. I don't know.

2 DR. BADEN: Dr. Giordano?

3 DR. GIORDANO: Switching topics a little  
4 bit, you mentioned the idea that penile  
5 transmission or acquisition seemed reasonably  
6 protected against here. Did the sponsor gather  
7 data on types of sex? Is there any signal that the  
8 acquisition was more likely in men who reported  
9 anal receptive versus anal insertive, or was there  
10 so much overlap between the two in any single  
11 person that you can't distinguish that?

12 DR. MIELE: My impression is that within  
13 each individual, there's a variety of sexual  
14 practices such that we can't really decipher  
15 whether there was a subgroup that was strictly  
16 practicing insertive sex. I believe pretty much  
17 all of the HIV seroconverters were practicing anal  
18 receptive intercourse. But that said, some of them  
19 also had reports of insertive sex in there.

20 There were individuals who reported -- for  
21 the most part, insertive sex had showed up with  
22 rectal STIs. And again, all these reports are

1 self-reported in the patient diaries. Like I said,  
2 I don't think we have any direct evidence. Given  
3 the low number of HIV infections, and the fact that  
4 we presume that a lot of these individuals were  
5 practicing insertive sex, that the protection  
6 probably did confer to them as well.

7 DR. BADEN: Dr. Daskalakis, a follow-on?

8 DR. DASKALAKIS: Just a brief follow-up,  
9 again, for clarification on this issue. If I  
10 remember, I think about 60 something percent of the  
11 folks in the DISCOVER trial were uncircumcised.  
12 Any special circumcision signal  
13 with seroconversion?

14 DR. MIELE: No. It was 44 percent.

15 DR. DASKALAKIS: Forty-four; sorry. I knew  
16 it was high.

17 DR. MIELE: Yes. No, in terms of baseline  
18 characteristics and HIV infection, we didn't see  
19 any real correlation.

20 DR. DASKALAKIS: I do remember the  
21 confidence interval for outside the U.S. was a lot  
22 higher. Is circumcision at all involved in that?

1 DR. MIELE: I have to defer to our  
2 statistician if you recall anything.

3 DR. BADEN: Please state your name at the  
4 microphone.

5 DR. ZENG: Wen Zeng, statistical reviewer  
6 for this NDA. For the subgroup analysis, I think  
7 the sponsor already presented. There's no such  
8 baseline characters that have a great impact on the  
9 final result.

10 DR. BADEN: Follow-on? Not a follow-on, a  
11 new topic.

12 Dr. Daskalakis, a new topic?

13 DR. DASKALAKIS: Yes, just a question about  
14 a citation that you had in your briefing document  
15 is a meta-analysis by Hale et al., that compares  
16 TDF, that compares tenofovir, and Truvada versus  
17 Descovy. Then subsequently, the safety data  
18 presented talks about statistically significant  
19 margins of safety.

20 Are any of these, from your perspective,  
21 clinically significant?

22 DR. MIELE: I think in the clinical setting

1 probably not, but over the long term they might be.  
2 I think the current average use of PrEP at this  
3 point is 6 to 12 months.

4 DR. DASKALAKIS: Just again, a quick  
5 follow-up on that.

6 DR. MIELE: Anyway, no. We didn't see  
7 anything different between the two arms in terms of  
8 clinical events.

9 DR. DASKALAKIS: If you stratify the bone  
10 and kidney complications or adverse events by age,  
11 is there anything that sort of flushes out in terms  
12 of just being more common among older adults?  
13 Because there are some 60 year olds and 50 year  
14 olds in the study.

15 DR. MIELE: There were a small number of  
16 older participants. We didn't see any differences  
17 come up on either end of the age spectrum.

18 DR. DASKALAKIS: Great. Thank you.

19 DR. BADEN: Dr Goetz?

20 DR. GOETZ: My question relates to the  
21 nature of risk in the patient population and the  
22 expected rate of HIV in the patient population. I

1 know the study was projected at a rate of infection  
2 that was somewhat higher. I wonder if someone from  
3 the agency could run through the calculations that  
4 predict what the expected rate of HIV infection was  
5 in the absence of a prophylaxis.

6 Taking to the extreme, if the study is done  
7 in a low-risk patient population, of course, no  
8 infections are expected, and the two agents perform  
9 similarly. So having confidence of the projections  
10 of what the expected rate of infection is, I think  
11 is an important consideration.

12 DR. MIELE: Do you mean without PrEP? This  
13 wasn't a placebo-controlled trial, so to that end,  
14 I think you're asking how would this compare. I  
15 think the applicant did do a comparison to local  
16 geographic areas in the U.S. based on  
17 epidemiological data, looking at concurrent HIV  
18 incidence in MSM not on PrEP. I think there were 4  
19 to 5 incidents per 100 person-years. At least in  
20 the U.S. population of MSM, in the geographical  
21 areas where this study was conducted, the incidence  
22 was much higher.

1 DR. BADEN: And the STI rate, how does that  
2 influence your thinking of being in a high-risk  
3 population?

4 DR. MIELE: Dr. Murray has published a meta-  
5 analysis looking at various PrEP trials, and trying  
6 to correlate the STI rate, at least for rectal  
7 gonorrhoea and what the predicted HIV incidence  
8 would be, as you heard, there was actually a high  
9 amount of STIs going on in this trial. And based  
10 on the correlations that we've looked at, that  
11 should have correlated to an HIV incidence, I  
12 believe, of 6; so a much higher incidence.

13 DR. BADEN: Six what? Six of a thousand?

14 DR. MIELE: Six per hundred.

15 DR. BADEN: Okay. So 10-fold higher.

16 DR. MIELE: Much higher.

17 DR. BADEN: If no other follow-ons, then I  
18 have another follow-on to Dr. Siberry's earlier  
19 comment. The issue of a trial in cisgender women,  
20 you mentioned that it was hard to come up with a  
21 noninferiority margin. Can you help us understand,  
22 does that mean it's not possible or how would you

1 frame a -- could that have been done or what might  
2 it look like for us to understand the challenges in  
3 a more fully powered trial?

4 DR. MIELE: The challenge is that we have  
5 two trials that essentially showed no effect in  
6 women, VOICE and FEM-PrEP. Then we have one trial,  
7 the Partners PrEP trial. That did show  
8 statistically significant protection, the TDF2  
9 trial I don't think was powered for efficacy but  
10 did show a point estimate that favored efficacy in  
11 women.

12 So when you have such divergent results from  
13 the historical trials, I think it becomes a  
14 challenge to try to come up with an NI margin. I  
15 don't know if the statisticians want to discuss  
16 this any further, but that is basically -- the main  
17 conundrum is that we would not be able to  
18 adequately construct an NI margin with such  
19 divergent variety in previous trials.

20 DR. BADEN: So in the MSM trans population,  
21 where we have consistent results with Truvad, then  
22 it's easier to design a trial that shows consistent

1 results.

2 DR. MIELE: Exactly.

3 DR. BADEN: And in cisgender women, where  
4 the data are very uneven, it's difficult to have a  
5 trial, but we should assume that it should work.  
6 I'm just trying to follow the logic that's being  
7 put before us.

8 DR. MIELE: I think a strict NI margin, a  
9 noninferiority trial, would be difficult to  
10 construct. That said, there might be other  
11 possible study designs such as comparisons to local  
12 HIV incidence in the population of study and the  
13 community it studied. These are novel study  
14 designs that we're grappling with ourselves in the  
15 agency, given that we have a product on the market  
16 that is highly effective.

17 DR. BADEN: Dr. Gripshover?

18 DR. GRIPSHOVER: What about a switch study?  
19 Is that something that the FDA would consider it  
20 would be appropriate? So if we have women who are  
21 already taking Truvada for PrEP, would that be a  
22 study design that could be considered flipping half

1 to TAF and going forward? You may not have a high  
2 incidence rate, but at least you're comparing it to  
3 an already approved drug.

4 I'm curious what the agency would think if  
5 that's a study design that would work since you  
6 don't have a noninferior number.

7 DR. MIELE: Yes. I don't know what the  
8 comparison would be in a switch study other than  
9 safety. We haven't really considered a switch  
10 study for a registrational study.

11 DR. BADEN: Dr. Green?

12 DR. GREEN: This is a direct follow-on. You  
13 can't easily come up with a strategy to give a  
14 noninferiority study, but there's no reason to  
15 presume that if you did a head to head, that it  
16 would be superior. And it also seems like it would  
17 be unethical to do a placebo study.

18 So you may be telling us that we're back to  
19 the argument of the sponsor, that there's no  
20 feasible way to assess it, so we have no choice but  
21 to make a decision using extrapolation. I don't  
22 know if that's your intent to say, but I'm hearing

1 that at least. Tell me why that's not true.

2 DR. MIELE: No. I think you've hit the nail  
3 on the head. The question is how confident do we  
4 feel that an extrapolation approach would be  
5 reasonable to extend the indication. At this  
6 point, we haven't really discussed any other  
7 alternative study design, so that may still be on  
8 the table. But where we are right now is you're  
9 right. And it's not a question of whether we think  
10 this is appropriate, but whether in the absence of  
11 other supporting data, we feel confident that this  
12 might work.

13 DR. BADEN: Dr. Ofotokun?

14 DR. OFOTOKUN: I don't seem to buy the  
15 argument that we cannot construct an inferiority  
16 margin around the data that we currently have for  
17 women because we know from looking at the data, and  
18 all the four studies in PrEP in women, the reason  
19 that those studies, where efficacy was not  
20 demonstrated was that way because of poor  
21 adherence.

22 So in studies where women took those drugs,

1 the drug was effective, and we can construct a  
2 margin around those studied. There's nothing that  
3 says that you have to include all the studies that  
4 have ever been done in order to construct an  
5 inferiority margin in the study design. I remember  
6 when the sponsor represented, they had a series of  
7 planned studies in women. So how are they planning  
8 to do that, if it's going to be impossible to have  
9 what is a sample size calculation for studies in  
10 women?

11 DR. MIELE: I'll answer your second part  
12 first. We have not seen any of these proposals in  
13 the agency that the applicant has proposed. We  
14 have not seen any protocols. My understanding is  
15 that these aren't going to be powered for efficacy  
16 comparisons. They may be safety demonstration  
17 projects.

18 To your first question, I think I'll defer  
19 to our statistician colleague about constructing an  
20 NI margin using just a select number of trials.

21 DR. BADEN: Please state your name.

22 DR. VALAPPIL: Yes. My name is Thamban

1 Valappil. I'm team leader for statistics. Based  
2 on the noninferiority guidance document that has  
3 been published, you need to have a clear evidence  
4 of treatment effect historically, meaning  
5 that -- especially for this population, there is no  
6 treatment effect compared to placebo. Both the  
7 studies have failed.

8           So unless you have a measurable treatment  
9 effect based on historical trials, you won't be  
10 able to construct a noninferiority margin. So the  
11 compliance or the adherence cannot be adjusted to  
12 be able to look at the margin if the plans have  
13 already failed.

14           DR. BADEN: Dr. Smith, you have a follow-on?

15           DR. SMITH: Yes. There's a lot of work  
16 going on to develop new agents for PrEP, for  
17 pre-exposure prophylaxis, and it's not clear to me  
18 whether you're saying that from now on, no studies  
19 will be done in women because we can't define the  
20 margin, and therefore we can't do a noninferiority  
21 trial.

22           The current PrEP is so effective, I don't

1 understand what the implications of this decision  
2 are for future trials. Given that, it may be  
3 difficult to find a high incidence population of  
4 women in the U.S. It's certainly not the case in  
5 the developing world, and I think, in fact, in the  
6 world at large, women are the largest number of new  
7 infections.

8           So the need for effective prevention options  
9 for women is even greater than for MSM, although  
10 not in this country. So if we're saying from now  
11 on that we'll do the studies in men and we'll do  
12 some PK studies to extrapolate to women, that  
13 doesn't sound like a good scientific approach. So  
14 I'm trying to understand the boundaries that you're  
15 drawing around this argument here and how that will  
16 apply in the future.

17           DR. MIELE: Yes, Dawn, we're not saying that  
18 at all. There is a path forward in terms of  
19 superiority designs. A lot of new agents that are  
20 being developed for PrEP are not necessarily  
21 once-a-day pills. The challenge here is we have  
22 two drugs that are very similar in terms of their

1 route of administration and their dosage.

2 If you're looking at long-acting agents, for  
3 example, you can do a superiority trial, so that's  
4 what we've been advocating. Again, like I said,  
5 this is a particular circumstance here that is  
6 complicated because we have two very similar  
7 products. But no, this PK extrapolation that's  
8 being proposed is not meant to be precedence  
9 setting for future trials in women at all.

10 DR. BADEN: We do need to remember that the  
11 business at hand is the current application. There  
12 are broader questions that I think are appropriate  
13 for us to highlight, as we've been doing, to set  
14 the stage for data in the future that are needed to  
15 make informed choices. So your points are very  
16 well taken. I'm not sure we'll resolve agency  
17 policy going forward, but I think the points have  
18 been heard.

19 Dr. Goetz, did you have a follow-on?

20 (Dr. Goetz gestures no.)

21 DR. BADEN: Dr. Giordano?

22 DR. GIORDANO: Can you clarify from the

1 agency's perspective how much of a study needs to  
2 be done in the U.S. versus abroad to achieve an  
3 indication?

4 DR. MIELE: The guidance suggests we can  
5 accept clinical data from foreign studies if the  
6 sponsor has provided a justification or rationale  
7 why that data are applicable to a U.S. population.  
8 In this case, 60 percent of the subjects were in  
9 the U.S., so I think we're covered.

10 I mean, it's not that preponderance of  
11 foreign data here. But for PrEP in general, for  
12 example, for women where most of these studies will  
13 be conducted ex-U.S., the mechanism of transmission  
14 of HIV and the mechanism of action for the drug  
15 should be the same regardless of the geographical  
16 populations.

17 DR. BADEN: Other questions for the agency  
18 about their presentation and their analyses of the  
19 data submitted?

20 (No response.)

21 DR. BADEN: If not, it is 12:20, and 12:25  
22 is when we're supposed to take a break. I don't

1 think we have enough time to delve into another  
2 line of questioning, but to the applicant, I think  
3 you've heard issues around, and perhaps after we'll  
4 do the open public session, and then we'll come  
5 back to clarifying questions to the applicant.

6 Crisp data on the efficacy in trans and  
7 crisp data on the insertive male partner, if you  
8 have it, were some of the issues raised that I  
9 think you have the data, and it would be just great  
10 for the committee to see.

11 Comments around the design issue in the  
12 cisgender female, which have come up, I think would  
13 be very helpful for the committee to hear your  
14 thoughts on that. You've touched on them, but I  
15 think they're central to our discussion. Then  
16 after lunch, we'll have the open public hearing  
17 session, and then resume the discussion with the  
18 applicant and the agency, but I think the agency  
19 has finished their clarifying component.

20 So we will now take a break for lunch.  
21 We'll reconvene again in this room at 1:30 sharp.  
22 Please take any personal belongings you may want

1 with you at this time. Committee members, please  
2 remember that there should be no discussion of the  
3 meeting during lunch amongst yourselves, the press,  
4 or any member of the audience. Thank you.

5 (Whereupon, at 12:20 p.m., a lunch recess  
6 was taken.)

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1                   A F T E R N O O N   S E S S I O N

2                                   (1:30 p.m.)

3                                   **Open Public Hearing**

4                   DR. BADEN: It is now 1:30, and we shall  
5 resume. This is now the open public hearing part  
6 of the meeting.

7                   Both the FDA and the public believe in a  
8 transparent process for information gathering and  
9 decision making. To ensure such transparency at  
10 the open public hearing session of the advisory  
11 committee meeting, FDA believes that it is  
12 important to understand the context of an  
13 individual's presentation.

14                   For this reason, FDA encourages you, the  
15 open public hearing speaker, at the beginning of  
16 your written or oral statement to advise the  
17 committee of any financial relationship that you  
18 may have related to the topic of the meeting.

19                   Likewise, FDA encourages you at the  
20 beginning of your statement to advise the committee  
21 if you do not have any such financial  
22 relationships. If you choose not to address this

1 issue of financial relationships at the beginning  
2 of your statement, it will not preclude you from  
3 speaking.

4 The FDA and this committee place great  
5 importance in the open public hearing process. The  
6 insights and comments provided can help the agency  
7 and this committee in their consideration of the  
8 issues before them. That said, in many instances  
9 and for many topics, there will be a variety of  
10 opinions.

11 One of our goals today is for this open  
12 public hearing to be conducted in a fair and open  
13 way, where every participant is listened to  
14 carefully and treated with dignity, courtesy, and  
15 respect. Therefore, please speak only when  
16 recognized by the chairperson. Thank you for your  
17 cooperation.

18 Will speaker number 1 step up to the podium  
19 and introduce yourself? Please state your name and  
20 any organization that you're representing for the  
21 record.

22 DR. HALL: Christopher Hall, San Francisco

1       AIDS Foundation. Good afternoon. In my capacity  
2       as vice president of medical affairs for the San  
3       Francisco AIDS Foundation, I oversee the provision  
4       of HIV pre-exposure prophylaxis through SFAF sexual  
5       health clinic, serving populations at high risk for  
6       HIV acquisition. Sorry. My disclosures are listed  
7       in the previous slide. Thank you.

8               To date, these programs have prescribed  
9       Truvada for PrEP to over 5,080 individuals. I will  
10       present our position in support of the proposed  
11       supplemental NDA by Gilead Sciences for the  
12       fixed-dose combination of emtricitabine and  
13       tenofovir alafenamide, which I will hereby refer to  
14       as F/TAF for HIV PrEP.

15               We believe that FDA approval of F/TAF as an  
16       additional PrEP option will expand the number of  
17       individuals who will choose to use PrEP as an HIV  
18       prevention method. And furthermore, F/TAF for PrEP  
19       will allow centers like the ones we operate to  
20       enroll more clients, especially those at higher  
21       risk for HIV acquisition.

22               Before I continue, for transparency, I will

1 state that where SFAF has received programmatic  
2 support from Gilead, accounting for less than 4  
3 percent of its total annual revenues in the last  
4 fiscal year, 3 percent of which are programmatic  
5 and 1 percent are research-related, this statement  
6 is derived in my own professional medical review in  
7 the position of the foundation leadership, and has  
8 in no way been influenced by Gilead or its staff.

9 SFAF enrolled 59 participants in the  
10 DISCOVER trial through May 2017. We understand  
11 that early results demonstrate a very low incidence  
12 of HIV in both treatment arms, only 7 infections in  
13 the F/TAF group and 15 in the Truvada group. Thus,  
14 we do not draw the conclusion that F/TAF is better  
15 than Truvada but agree that it is shown to be at  
16 least as good as Truvada for preventing HIV.

17 In addition, preliminary DISCOVER data  
18 suggests better renal and bone outcomes for those  
19 participants on F/TAF, that we agree with the  
20 interpretation that such improved outcomes are  
21 likely marginal in significance. Yet, based on  
22 remote and recent understanding of motivators for

1 PrEP engagement, we believe individuals at risk for  
2 HIV, including those most at risk such as black and  
3 Latino persons, may be more likely to engage with  
4 PrEP, as more agents with improved side effect  
5 profiles are available for approved use.

6           Additionally, F/TAF offers a PrEP  
7 alternative for those who have compromised renal  
8 function who cannot use Truvada for PrEP. As 12  
9 percent of our PrEP patients are over 50 and thus  
10 more likely to present with comorbidities,  
11 including preexisting renal compromise or  
12 osteopenia, an agent with a marginally better side  
13 effect profile may promote engagement, and in fact  
14 be meaningfully safer.

15           A strategic priority of the foundation is to  
16 center its prep services on communities  
17 disproportionately faced with alarming HIV  
18 incidence rates, and this includes Black Americans.  
19 Our recent efforts enrolling such persons on PrEP  
20 have demonstrated the need for new approaches and  
21 tools.

22           As black and African Americans face over

1 3 times the rate of kidney failure in the U.S.  
2 compared to Caucasians, choice of a PrEP agent with  
3 a marginally improved renal safety profile may  
4 predispose engagement based on both real and  
5 perceived advantages.

6 The approval of F/TAF may also enhance  
7 programmatic capacity to provide expanded PrEP  
8 services at CBOs like ours. PrEP service delivery  
9 is affected by local and/or other structural  
10 factors such as depicted hopefully here.

11 Innovation of an express model of STI  
12 screening supporting clinical PrEP follow-ups, in  
13 2018 facilitated sustained increases in our program  
14 capacity and was associated with an approximate 30  
15 percent increase in the number of active PrEP  
16 patients.

17 Clinical management of PrEP patients using  
18 Truvada requires renal function and monitoring,  
19 including a baseline check and others every 3 to  
20 6 months. In our setting, that includes confirming  
21 creatinine elevations with a secondary point of  
22 care assay, and in some cases scheduling earlier

1 and/or closer follow-up for those evidencing such  
2 elevations. In the last year, for example, 1 in 15  
3 clients required additional laboratory tests and/or  
4 intensive follow-up while on Truvada.

5 With conventional use of F/TAF as an  
6 antiretroviral, a lower threshold of diminished  
7 renal function is tolerated before recommended  
8 discontinuation. We believe that we can project a  
9 more streamlined renal function monitoring  
10 algorithm with use of F/TAF for PrEP, and in turn  
11 an ability to follow more individuals on PrEP with  
12 decreased laboratory expenditures, less intensive  
13 lab monitoring, and fewer staff resources dedicated  
14 to closer follow-up demanded by present use of  
15 Truvada alone.

16 With all other circumstances held unchanged,  
17 F/TAF, if approved for use and prescribed for a  
18 portion of our PrEP patients, we project a future  
19 internal PrEP capacity increased based on these  
20 renal monitoring factors alone such that we can  
21 enroll and follow an estimated 10 to 15 percent  
22 more individuals on PrEP in the first year.

1           Features of U.S. PrEP programs vary, but the  
2 foundation believes that the impact of F/TAF's  
3 introduction as the second FDA-approved agent  
4 indicated for PrEP will lead to meaningfully  
5 enhanced capacity to reach more individuals in need  
6 of this proven biomedical HIV prevention  
7 intervention, especially African American, Latino  
8 individuals served by the foundation, and  
9 elsewhere. Thank you for your time and attention.

10           DR. BADEN: Thank you. Will speaker number  
11 2 step up to the podium and introduce yourself?  
12 Please state your name and any organization you're  
13 representing for the record.

14           DR. FOX-RAWLINGS: Thank you for the  
15 opportunity to speak today on behalf of the  
16 National Center for Health Research. I am  
17 Dr. Stephanie Fox-Rawlings. Our center analyzes  
18 scientific and medical data to provide objective  
19 health information to patients, health  
20 professionals, and policymakers. We do not accept  
21 funding from drug or medical device companies, so I  
22 have no conflicts of interest.

1           A new treatment to prevent HIV infection  
2 could be beneficial considering the safety concerns  
3 of the currently available PrEP treatment.

4           However, Descovy would only provide benefit if it  
5 is at least as effective and safe as Truvada for  
6 each population for which it is indicated.

7           Otherwise, users could be at an unnecessarily  
8 increased risk for HIV.

9           The DISCOVER trial found similar rates of  
10 protection against HIV infection among participants  
11 taking both drugs. While the trial seems well  
12 designed to demonstrate comparable effectiveness of  
13 these two drugs, it is still a single trial.

14           Replication is a key to scientific evidence, and  
15 independent trials could result in different  
16 infection rates due to differences in demographic  
17 or treatment profiles of patients or other factors.

18           For example, study participants were more  
19 likely to be white, older, and better educated than  
20 the general U.S. population that is at risk for  
21 HIV, which is the target audience for the drug.  
22           While this population may be consistent with the

1 people who are currently using Truvada, there are  
2 questions about the generalizability of the data to  
3 the whole population who could consider using this  
4 drug. It is important to study the general U.S.  
5 population that is at risk for HIV.

6 The study also found improvements for  
7 biomarkers related to kidney health and bone  
8 density, suggesting that this was safer than  
9 Truvada, however, this is only relevant if it  
10 translates into clinically meaningful difference in  
11 the number of adverse events related to kidneys or  
12 bone fractures, which were similar in both  
13 treatment groups in the clinical trial.

14 The trial suggests that the benefits  
15 outweigh the risks for men who have sex with men.  
16 However, the benefit-risk ratio was less clear for  
17 transgender women. This is due in part to the  
18 relatively low number of transgender women in the  
19 trial, the high dropout rate, and the lack of  
20 subgroup analysis. If FDA is considering approving  
21 Descovy for transgender women, then the efficacy  
22 and safety of the drug for transgender women should

1 be analyzed.

2 This is especially important given the  
3 recent finding that feminizing hormone therapy can  
4 interact with PrEP drugs. Similarly, there is  
5 insufficient evidence that the drug is effective  
6 and safe for PrEP for cisgendered women or  
7 adolescents.

8 There are too many unanswered questions  
9 regarding the levels of drug achieved, and relevant  
10 tissues, and the amount needed in these tissues to  
11 consider extrapolation for PrEP for use for  
12 cisgendered women and girls.

13 Similarly, the benefits and the risks for  
14 adolescent boys differ from that of men and should  
15 be considered separately. Clinical trials  
16 demonstrating effectiveness and safety for  
17 cisgendered women and adolescents are needed if the  
18 FDA is considering approval for them.

19 We understand the desire to provide a new  
20 PrEP treatment indicated for a broad population,  
21 especially when a new treatment may be expected to  
22 have fewer risks for kidneys and bone density.

1       However, it is inappropriate and potentially  
2       dangerous to approve this drug for subgroups of  
3       patients that haven't been adequately studied. The  
4       FDA law requires substantial evidence that benefits  
5       outweigh the risks for each subpopulation, and the  
6       new indication would include. Thank you.

7               DR. BADEN: Thank you. Will speaker number  
8       3 step up to the podium and introduce yourself?  
9       Please state your name and any organization you're  
10      representing for the record.

11             MS. JOHNSON: Thank you so much. My name is  
12      Jeremiah Johnson. I'm the HIV project director at  
13      Treatment Action Group in New York. We appreciate  
14      that this hearing is being held today. Considering  
15      how centrally Gilead has controlled this entire  
16      process around TAF development, all the way from  
17      delaying it for a decade when they purported safety  
18      and preventive benefits for this medication; all  
19      the way to centrally controlling the DISCOVER trial  
20      without adequate participation of community; all  
21      the way to rushing us through this regulatory  
22      process, we believe it is extremely important that

1 this regulatory agency and the community be given  
2 time to have a transparent discussion about this,  
3 and for us to take control of this process again,  
4 and away from an applicant that has a vested  
5 interest in maintaining a \$2 billion a year market  
6 in biomedical prevention in the U.S.

7           You may be familiar with TAG's work on  
8 hepatitis C and tuberculosis as well. That's a  
9 little bit about us. Within my 6 remaining  
10 minutes, I'm going to go over three main points in  
11 a small amount of time, so please pay attention.  
12 To start, we're going to be talking about what  
13 we've been talking about a lot here today in terms  
14 of representation within DISCOVER and within the  
15 broader body of evidence that we have as part of  
16 this sNDA discussion today.

17           We have a number of concerns about Gilead's  
18 active campaign against its own product, Truvada,  
19 and what will be generic TDF/FTC PrEP within the  
20 next year, and overstatement of efficacy and safety  
21 benefits of Descovy compared to that, and have a  
22 general discussion about the lack of transparency

1 in this whole process and a rushed process when  
2 these involve important discussions that clearly  
3 the community was not adequately consulted on early  
4 on in the process.

5 I won't go into this slide too much.  
6 Obviously, the trial participants within the  
7 DISCOVER trial do not represent the broader  
8 epidemic that we see in the United States and  
9 around the world. With 84 percent of trial  
10 participants being white and 99 percent being  
11 cisgender men, and only 74 participants identifying  
12 as transgender women, clearly we are not seeing a  
13 body of evidence that is reflective of all  
14 populations that need to be considered in terms of  
15 efficacy, safety, and effectiveness for scale up of  
16 a new prevention option.

17 Right now, you're hearing here at this  
18 podium, and there's a lot of discussion online  
19 right now, there's a lot of debate amongst  
20 community advocates about what does this data mean  
21 and what should we be advocating for considering  
22 that we don't have sufficient data? And for no

1 good reason do we have insufficient data.

2 Some of us believe that we have to continue  
3 to advocate for an indication for cisgender women  
4 because we don't believe that the company sees it  
5 as beneficial to their bottom line to do the  
6 follow-up efficacy research in order to get an  
7 indication for cisgender women. And if we miss out  
8 on this opportunity, then there will be PrEPs for  
9 different populations, and that's clearly a  
10 problem.

11 But at the same time, we're concerned that  
12 we're sending a message. Dr. Smith's comment  
13 earlier was well taken that we're sending a message  
14 that if we don't do adequate research within these  
15 populations, that you don't have to do that, and  
16 you can get a broader indication anyway, and that's  
17 an enormous problem.

18 So it's up to the FDA here today and going  
19 forward in this discussion whether you believe that  
20 the information and the evidence presented thus far  
21 is indicative of a broader indication or a narrow  
22 indication. But what must be clear is that

1 cisgender women cannot be left behind; neither can  
2 any of the populations that have been left behind  
3 in this entire process.

4 If it is not approved with a broad  
5 indication, there must be a guarantee and there  
6 must be requirements that the company continues to  
7 fund efficacy, effectiveness, and safety studies  
8 within cisgender women so that they are not left  
9 behind in this process.

10 If it is approved, it needs to be contingent  
11 upon open-label studies that continue to give us  
12 more information for that population. That is  
13 essential, and it must happen, and this regulatory  
14 body needs to make up for the deficit of actions  
15 that took place earlier in this process. We also  
16 need to see that for all of the communities that  
17 are highly prioritized within our broader epidemic  
18 work but were not prioritized within this research.

19 In terms of efficacy, DISCOVER was a  
20 noninferiority trial. We are very aware that  
21 Gilead is trying to paint Descovy as a superior  
22 option in terms of efficacy. That is not borne out

1 in the evidence, and it stands to sabotage scaling  
2 up of generic TDF/FTC next year, and to generally  
3 sabotage Truvada's scale up for individuals who are  
4 already stably avoiding HIV infection on that  
5 regimen when there is no medical or efficacy  
6 related reason for them to switch over.

7 They're also trying desperately to, even in  
8 this room today, boldly assert that it is a safer  
9 option when in fact we do not see clinically  
10 different outcomes in the DISCOVER trial, and in  
11 fact they continue to downplay statistically  
12 significant increases in weight and challenging  
13 issues around lipids that certainly indicate that  
14 it is not necessarily a safer option.

15 It is important that this regulatory body  
16 operate with the highest level of scrutiny with the  
17 labeling, with the marketing, and with the  
18 educational materials that come out of the  
19 applicant should an indication be provided for  
20 Descovy as PrEP.

21 Just quickly, these are slides that of  
22 course Gilead will not be presenting today, but we

1 saw from the DISCOVER trial that there was a  
2 statistically significant increase in weight in the  
3 TAF arm. And of course in terms of treatment, we  
4 are seeing a disproportionate impact on weight  
5 within cisgender women and individuals of African  
6 descent, which further stresses the need for  
7 additional research in those populations  
8 considering that the DISCOVER trial was not  
9 representative of these populations.

10 Ultimately, we have to ask what is the rush  
11 in this entire situation. There's not one  
12 peer-reviewed publication that has come out of the  
13 DISCOVER trial. There is little transparency.  
14 Today, we are just starting to see some of the  
15 information from the trial. And all of this is  
16 coming after a decade of delaying TAF development.  
17 We are frustrated as community members that Gilead  
18 continues to centrally control this process, the  
19 FDA does not, and that community has not been  
20 adequately involved.

21 So going forward, this body needs to send a  
22 clear signal that any manufacturer engaging in the

1 field of biomedical prevention research must do a  
2 better job. They actually have to adhere to GPP;  
3 they actually have to work with community from the  
4 start; and they actually have to allow this  
5 regulatory body to come up with a robust research  
6 protocol that covers all populations and not just  
7 their bottom line.

8 So with that, I will close in just saying  
9 that we require robust postmarketing research  
10 following this discussion today, that the labeling  
11 and all materials need to be under high scrutiny,  
12 and that we need a clear message from the FDA that  
13 this process will go better in the future with  
14 future provincial modalities. Thank you.

15 DR. BADEN: Thank you. Will speaker  
16 number 4 step up to the podium and introduce  
17 yourself. Please state your name and any  
18 organization you're representing for the record.

19 MR. KRELLESTEIN: Hello. My name is James  
20 Krellestein. I am a cofounder of the PrEP4All  
21 collaboration. We are an all-volunteer group of  
22 activists who are dedicated to ensuring universal

1 low-cost access to HIV-1 pre-exposure prophylaxis.

2 I just wanted to review, before we  
3 begin -- next slide, please -- what Descovy is.  
4 Descovy of course is a co-formulation of two  
5 different drugs, tenofovir alafenamide fumarate,  
6 which was first approved back in 2015 as part of  
7 Genvoya, a fixed-dose, single-tablet regimen for  
8 HIV treatment, and emtricitabine, which was first  
9 FDA approved as Emtriva back in 2002.

10 One of the things that has been talked about  
11 extensively today is that tenofovir alafenamide has  
12 some alleged advantages over tenofovir disoproxil,  
13 which is that the prodrug catabolism occurs  
14 intracellularly rather than tenofovir disoproxil,  
15 which is actually metabolized primarily  
16 systemically, allowing lower plasmic exposures to  
17 tenofovir but higher levels of tenofovir  
18 diphosphate, the pharmacologically active  
19 anabolite, compared to tenofovir disoproxil, at  
20 least in PBMCs. This is alleged to convey certain  
21 safety benefits compared to TDF.

22 I think that one of the things that's really

1 important, though, to realize in this entire  
2 process is that TAF is not a new drug despite being  
3 FDA approved in 2015. In fact, Gilead first filed  
4 a patent application for TAF, claiming priority all  
5 the way back to 2000, using of course its code name  
6 at that time as GS7340. And of course, Gilead  
7 scientists published a peer-reviewed scientific  
8 journal in nucleosides, nucleotides, and nucleic  
9 acids, all the way back in 2001 regarding the  
10 metabolism of GS7340 now known as TAF.

11 I think the question that we should all be  
12 asking ourselves is two things. First of all, why  
13 in 2019 are we discussing an FDA application for  
14 F/TAF as PrEP? And number two, why don't we have  
15 better data on cisgender women?

16 Had F/TAF actually been developed when it  
17 was supposed to be developed, we would have had an  
18 F/TAF arm in iPrEx. We would have had an F/TAF arm  
19 in Partners PrEP. We would have high-quality,  
20 randomized-controlled evidence in all populations  
21 that are being sought in indication for today.

22 So let's go through the development of TAF,

1 if you would. Gilead began early phase 1 and phase  
2 2 trials back in 2001 and 2002 and filed an IND  
3 with this agency for the development of TAF back in  
4 January of 2002. But in October 23, 2004, they,  
5 based on an internal business review, discontinued  
6 development of TAF, only on October of 2010 to  
7 restart development of TAF.

8 What was the reason for this stop-start  
9 approach to drug development? You don't have to  
10 look to me, you don't have to look to Jeremiah, and  
11 you don't have to look to anyone in this room to  
12 actually understand what Gilead was doing. You can  
13 look to their former CEO, Dr. John Milligan, who  
14 stated that "one of the reasons why we were  
15 concerned about developing TAF was we were trying  
16 to launch Truvada versus Epzicom at the time. And  
17 to have our own study suggesting that TDF wasn't  
18 the safest thing on the market, which it certainly  
19 was at the time, it didn't seem like the best. It  
20 didn't seem like we would have a mixed message."  
21 That was in 2011.

22 So as someone who takes TDF every single

1 day, I have to say I'm highly disturbed by the  
2 applicant's behavior to basically delay a drug that  
3 they knew was going to present at least some safety  
4 benefits compared to TDF, to protect their bottom  
5 line rather than to protect the public health, and  
6 I only wish that the FDA would share that very same  
7 feeling. But instead, the FDA rewards Gilead's  
8 decision to delay.

9 First of all, I was quite surprised by Dr  
10 Murray's statement that TAF is similar to TDF, or  
11 at least that it has the same active moiety as TDF  
12 considering that the FDA had granted TAF new  
13 chemical entity exclusivity in 2015, which prevents  
14 any challenges through the patent paragraph 4  
15 process until this year. It also recommended that  
16 the USPTO give the maximum patent term adjustment  
17 allowable under U.S. law, counting the entire  
18 period of Gilead's delay as a testing phase. This  
19 will prevent Americans from accessing generic  
20 Descovy for an additional five years.

21 I think it is an extraordinarily disturbing  
22 precedent that the Food and Drug Administration is

1       rewarding the decision of a corporation to delay  
2       the development of a drug that it is now purporting  
3       is safer than TDF/FTC.

4               As a final note, I will say that we are  
5       placed today -- this entire committee is placed  
6       today -- in an incredibly difficult position. We  
7       are basically placed with a catch-22. Either on  
8       one hand we deny the ability for Descovy or TAF/FTC  
9       from getting a broad indication for cisgender women  
10      and other populations, and despite having no  
11      effective efficacy data for this population, or we  
12      choose to deny the extension of that indication.  
13      That, unfortunately in today's environment, would  
14      basically work to deny women the choice to make the  
15      decision of the drug that they would like to take.

16             I believe personally, and not representing  
17      my organization, that the right choice is to extend  
18      the indication of F/TAF to cisgender women. But I  
19      have to admit that I am incredibly disturbed by the  
20      precedent that that would set. We have to say,  
21      today and more than two decades after AIDS  
22      activists seized control of both the Food and Drug

1 Administration and the Centers for Disease Control  
2 and Prevention, that cisgender women get HIV.

3 More than 50 percent of global infections  
4 are in cisgender women, and the idea that an  
5 applicant would decide not to basically provide  
6 high-quality evidence supporting efficacy in this  
7 population is disturbing. The fact that this  
8 agency may be forced to grant a broad indication  
9 with no efficacy data is also disturbing, and this  
10 can never happen again.

11 I want to make that incredibly clear.  
12 Cisgender women, transgender women, transgender  
13 people, men who have sex with men, all of us  
14 deserve -- that medical technologies that are  
15 scaling up to fight one of the deadliest pandemics  
16 of our time, they deserve high-quality evidence,  
17 and we should never again encourage companies to  
18 delay the development of innovative technologies,  
19 and we should never allow them, once again, to not  
20 provide high-quality evidence for these very  
21 important technologies. Thank you.

22 DR. BADEN: Thank you. Will speaker number

1 5 step up to the podium and introduce yourself?  
2 Please state your name and any organization you're  
3 representing for the record.

4 DR. GIPSON: Hello. June Gipson, CEO of my  
5 Brother's Keeper in Open Arms Health Care Center  
6 located in Jackson, Mississippi. My Brother's  
7 Keeper is a community-based organization with a  
8 mission to reduce health disparities throughout the  
9 United States by enhancing the health and wellbeing  
10 of minorities and marginalized populations through  
11 the leadership in public and community health  
12 practices, collaboration, and partnerships.

13 We do it through an array of programs and  
14 services, including our center for community-based  
15 programs, and we also have a center for research  
16 evaluation and policy change. One of our most  
17 prominent centers is going to be Open Arms Health  
18 Care Center. That's our primary healthcare clinic.

19 Open Arms Health Care Center is an  
20 innovative, holistic, primary healthcare clinic  
21 that offers preventive clinical mental health  
22 services to underserved, uninsured,

1 underrepresented populations with an emphasis on  
2 the LGBT population. We utilize a community-based  
3 model that's a community health team led approach  
4 to provide services to our clients that optimizes  
5 their healthcare. We provide an array of services,  
6 including women's health, family planning, men's  
7 health, PrEP, HIV care, mental health, preventive  
8 screenings, transportation, and emergency food  
9 assistance.

10           When you look at our HIV and PrEP in  
11 Mississippi, we've struggled, but we've been able  
12 to accomplish some things. If you look at our  
13 linkage for HIV testing and linkage to care, we're  
14 either exceeding or we're meeting the national  
15 goals. However, we continue to struggle in  
16 retention and care and viral suppression.

17           When you look at our PrEP data, this is data  
18 from Open Arms Health Care Center. This data is of  
19 particular interest because we provide 75 percent  
20 of all the PrEP in the state of Mississippi. As  
21 you can tell, it's sparse. We are not hitting the  
22 entire state. You have one red spot in the center

1 that really optimizes and says who we're reaching,  
2 so we have more to do. There are multiple reasons  
3 why we aren't able to do this in Mississippi.  
4 We've done assessments with our patients and our  
5 staff, and of course there's a lack of access.  
6 That's a prevalent thing; it's around the country.

7 We also have a stigma. Stigma exists in  
8 every form of HIV care that we provide. There's  
9 also some other concerns that have come up  
10 throughout our assessments with our patients. Not  
11 only is there a low perception of risk -- and you  
12 would think in Mississippi that that wouldn't be  
13 the thing, but it is -- but there's also a concern  
14 about side effects.

15 When you live in a state like Mississippi,  
16 side effects are huge because we are already  
17 existing with so many other negative health  
18 outcomes. When we see the commercials that talk  
19 about the benefits of the medication and how  
20 wonderful they are, and that last 15 seconds when  
21 they run through all of the side effects, that's  
22 what we hear. And I hear it in particular when you

1 speak about Truvada because my dad is on dialysis.  
2 My uncle is on dialysis. My cousin's on dialysis.  
3 So we're living the side effects, and we need a  
4 safer option.

5 We need a safer option for no other reason  
6 that we have gone through enough. We have high  
7 diabetes rates, high blood pressure rates, kidney  
8 failure; you name it, we have it, and all of this  
9 combined with HIV. We need Descovy for PrEP so we  
10 can increase utilization. If we gave pills free to  
11 everyone, that's access, but access is not  
12 indicative of utilization.

13 So we need to have a safer option for our  
14 community, and particularly with African Americans.  
15 Again, we live these health disparities. We live  
16 these side effects. And with women in particular  
17 who may have a low perception of risk, it seems as  
18 if we're taking Truvada, we're trading illnesses.  
19 I get rid of one just to get a another? That's not  
20 something that we want.

21 Particularly for adolescents, and I'm going  
22 to include parents with our adolescents, parents

1 generally want the best for their children. And  
2 they really don't want to think about their kids  
3 having sex, but we know that that's a real thing.  
4 But if they see the advertisements for Truvada, and  
5 they see the side effects, it gives an impression  
6 that they're going to expose their children to  
7 something that's going to give them a lifelong  
8 problem.

9           When you're in the state of Mississippi, you  
10 see your family in a dialysis clinic. If you ever  
11 have an opportunity come and visit, stop by a  
12 dialysis clinic. You'll see that it's filled with  
13 African Americans.

14           As it relates to adolescence, I actually  
15 have a call tomorrow with a parent. Her  
16 16-year-old son came to us. He tested positive for  
17 syphilis and chlamydia. We put him on PrEP. She  
18 called a month later wanting to take him off of  
19 PrEP because she's so concerned with the health  
20 issues and the side effects associated with PrEP.  
21 Now, you and I, we understand the correlation  
22 between syphilis and HIV, but that's not her

1 reality. That's not her perception. And we all  
2 live within our perception because that's our true  
3 reality. So I will like for Descovy to be approved  
4 for PrEP for utilization broadly between African  
5 American women and adolescents.

6 DR. BADEN: Thank you. Will speaker number  
7 6 please step up to the podium and introduce  
8 yourself? Please state your name and any  
9 organization you're representing for the record.

10 MR. MYERS: Good afternoon. I'm Kirk Myers  
11 of Abounding Prosperity in Dallas, Texas. I am the  
12 founder and chief executive officer of an HIV and  
13 AIDS prevention agency in Dallas, Texas. The  
14 mission of my organization is to provide services  
15 that address health, social, and economic  
16 disparities among Black Americans with an emphasis  
17 on the LGBTQ community and their families.

18 I'm also a black man who has sex with men,  
19 MSM, and who is living with HIV for over 26 years.  
20 Through my lived experiences and managing my own  
21 disease, and the leadership experience of managing  
22 my agency, dedicated to decreasing new incidence of

1 HIV and AIDS via various prevention programs, I  
2 know the delays and deliberations that are  
3 surrounding the prompt approval of Descovy for the  
4 proposed use of PrEP for black women, MSMs, and  
5 trans individuals is out of sync with our  
6 real-world reality.

7 For me, the simple language that best  
8 captures the reality among my people, especially  
9 those black women, MSMs, and trans individuals, is  
10 overwhelmed by the social, economic, and health  
11 disparities that they confront daily. So while  
12 some people have privilege on their side for  
13 time-consuming contemplation over the prompt  
14 approval of Descovy for the proposed use of HIV as  
15 PrEP, my community makes immediate choices on a  
16 day-to-day basis that ultimately could result in  
17 the acquisition or spread of HIV-AIDS.

18 Therefore, I urge the prompt approval of  
19 Descovy for the proposed use of HIV PrEP because it  
20 is right to give black women, MSMs, and trans  
21 people the option to make a safer effective choice  
22 on a daily basis to protect their lives as they go

1 about their business as usual. Whether their  
2 business is at the level where I work as the CEO or  
3 the street level of a sex worker, I will be  
4 standing as an authentic voice to compel the  
5 advisory community to consider the fact that I have  
6 immediate access to those who would benefit from  
7 Descovy for the proposed use of HIV prevention.

8 I have organized community forums, focus  
9 groups, and one-on-one individual level  
10 interventions to speak with authority that this  
11 drug is wanted. The young women and gay men who  
12 confide in me have expressed receptivity to a drug  
13 that has the potential to protect them from HIV-  
14 AIDS with lower side effects.

15 Finally, if anything is right at this  
16 historical moment in HIV prevention efforts, it is  
17 options to go beyond the past practice of  
18 normalizing the majority and ignoring the pressing  
19 needs of the minority. The right thing to do is to  
20 empower black women, MSMs, and trans individuals  
21 with the additional tools on a daily basis that are  
22 purposefully designed to protect public health.

1 Without this option, expediency, desperation, and  
2 ignorance will continue to drive up the statistics  
3 of new incidence of HIV and AIDS

4 With all due respect, I am asking the  
5 advisory committee members to join me in doing the  
6 right thing and assist on the prompt approval of  
7 Descovy for the proposed use of HIV-based  
8 prevention on my intimate relationships with MSM  
9 and transgender individuals, who expect me to speak  
10 out and share our testimony. This is the right  
11 step.

12 Furthermore, we implore that this drug be  
13 approved not just in gay men and transwomen, but  
14 women need this drug, and it will not be in the  
15 interest of public health to have this drug  
16 approved without including women, and to then be  
17 further stigmatizing by being looked at as a gay  
18 drug. Everyone deserves the same choices of  
19 prevention options as the rest of us.

20 Now, as a black man living with HIV here in  
21 America  
22 for the past 26 years, there has been this divide

1 between black gay men and black women, and when we  
2 look at our options, this is the best option for  
3 all of us possible. I'm not a scientist. I didn't  
4 have all the beautiful slides and all those things  
5 to compel you to do anything, but I can tell you  
6 from the grassroots level and at the street level  
7 that this drug is needed. And again, if we only  
8 approve it for one indication, it's going to create  
9 further stigma that we do not need. Thank you.

10 DR. BADEN: Thank you. Will speaker number  
11 7 step up to the podium and introduce yourself?  
12 Please state your name and any organization you are  
13 representing for the record.

14 MR. WARREN: Good afternoon. My name is  
15 Mitchell Warren, and I'm the executive director of  
16 AVAC, a New York-based global, nonprofit  
17 organization focused on accelerating the  
18 development and delivery of new prevention options.  
19 We take no money from any pharmaceutical companies,  
20 including from Gilead Sciences, although I should  
21 note I was a member without any compensation of the  
22 Independent Data Committee of the DISCOVER trial.

1 I stood here, as some of you in this room  
2 did as well, seven years ago, and the task was  
3 easy. The data was robust, the evidence was clear,  
4 and I'm delighted that that committee then, and the  
5 FDA shortly thereafter, followed the evidence and  
6 approved TDF/FTC for oral PrEP for all populations.

7 I wished the task were as easy today.  
8 There, while the evidence was clear, today we sit  
9 in somewhat of an evidence-free zone, at least in  
10 some areas as has been well discussed today. It's  
11 a dynamic space and one that I hope we don't return  
12 to ever again, and I have some thoughts about that  
13 toward the end. But the data are the data, and we  
14 must act on that most urgent data point presented,  
15 and that is an epidemic that continues in multiple  
16 places, in multiple populations. And what we do  
17 today matters, not just in the United States, but  
18 particularly for women at great risk of HIV  
19 infection in Africa.

20 I recognize full well that that is outside  
21 of the purview of the FDA and certainly of this  
22 committee. Your job is to look at safety and

1 efficacy for the United States. That said,  
2 decisions made in this room today, recommendations  
3 made in this room, decisions made subsequently by  
4 the FDA, will resonate and influence the global  
5 response. And I realize that's a heavy burden, but  
6 one that is real.

7 I'm going to take just a few minutes to go  
8 through the two questions that you have on the  
9 table, F/TAF for PrEP for men and transgender  
10 women, first and foremost. It is very clear to me  
11 and to AVAC, the organization I lead, that the data  
12 presented in the application does indeed support a  
13 noninferiority claim for F/TAF compared to F/TDF  
14 for oral PrEP for gay men and transgender women.

15 I emphasize that as noninferiority. The  
16 DISCOVER trial was set out to design for  
17 noninferiority, and it certainly met that task. I  
18 think that's a very important point not only as you  
19 make your vote today in the committee, but as the  
20 FDA works around the labeling with Gilead, that  
21 this be very clearly registered as a noninferior  
22 oral PrEP option.

1           Any claims of superiority I think are  
2 unfounded. Yes, there's a different safety  
3 profile, and we saw data today that made it seem  
4 both safer on some level but concerns in others  
5 with lipid and weight gain. But we need to be very  
6 clear so there is no confusion to PrEP users today  
7 on TDF/FTC, or PrEP users of tomorrow that we are  
8 somehow promoting one as a safer and more effective  
9 drug. This is a noninferior oral PrEP option, and I  
10 support that wholeheartedly, but all labeling must  
11 be consistent with that and be strongly enforced.

12           In terms of the second question you all will  
13 consider, it's perhaps the more challenging in so  
14 many respects, and that is F/TAF for cisgender  
15 women. It is extremely unfortunate that similar  
16 safety and efficacy data for F/TAF were not  
17 collected in an efficacy trial. We can spend a lot  
18 of our time Monday morning quarterbacking why that  
19 was and why decisions were made.

20           I would argue that the best time to debate  
21 that is not sitting in an FDA hearing to consider a  
22 drug approval. Those should've been open

1       conversations we had with the company, with the  
2       FDA, and with community groups far and wide to  
3       discuss the best pathway for product development.  
4       I do trust that that is the case, and I think  
5       Dr. Murray in his introductory comment described  
6       that for next generation new chemical entity PrEP  
7       agents. That is not a change; that what we  
8       discussed today is not creating a new status quo.  
9       We do have to recognize that this is a tenofovir  
10       prodrug and tenofovir-based prep, and I use my  
11       comments in that regard.

12                If F/TAF is not extended to include  
13       cisgender women, the one group, the only group that  
14       will suffer and pay the price for that decision are  
15       women at risk of HIV infection. The FDA won't  
16       suffer, Gilead will not suffer, and other agencies  
17       will not suffer. That said, we have to always be  
18       clear that safety and efficacy matter.

19                Based on the data presented today, and I  
20       should say in addition, not taking money from  
21       pharmaceutical companies. I am not a statistician,  
22       a trialist, an ethicist, or scientist of any type.

1 I'm an advocate. But I will say that based on the  
2 data presented here, recognizing the systemic  
3 levels as monitored in a range of studies both for  
4 the safety study presented, although less robust  
5 than we would like, as well as the treatment  
6 studies, there's a very clear rationale for F/TAF  
7 to work as well as F/TDF in women.

8 I believe that that is critical to approve.  
9 That said, I believe that that PrEP indication  
10 needs to come with an incredibly strong, robust,  
11 and enforceable postmarketing surveillance,  
12 research agenda, and a risk evaluation mitigation  
13 strategy that makes it very clear that over the  
14 next 12 to 24 months, Gilead will be responsible  
15 for collecting, in collaboration with other  
16 research groups, the relevant data for safety and  
17 effectiveness.

18 As well discussed here, efficacy of PrEP in  
19 women is hard to measure currently with oral prep;  
20 not impossible, but hard to do. Let us focus on  
21 effectiveness, and let us ensure that an  
22 FDA-enforced postmarketing surveillance in REMs

1 ensures that we have that data.

2 I will say, too, in our work, in Africa  
3 particularly, and has been reported in a number of  
4 studies, including work that we have done, that  
5 pill size does matter. It is one of the leading  
6 reasons that women in programs in Africa talk about  
7 not continuing with F/TDF. While again, I realize  
8 Africa is not in the purview of this committee or  
9 of the FDA, your decision will matter, and a  
10 smaller drug, not necessarily safer or more  
11 effective, but a smaller drug will be of enormous  
12 benefit.

13 I want to emphasize again in closing that  
14 the education prescriber information and supportive  
15 materials that are part of any package going  
16 forward with F/TAF need to be heavily monitored by  
17 the FDA, and not just between the FDA and Gilead  
18 but with community input; not tokenistically, but  
19 in an active way to ensure that the language used  
20 to describe this indication as a noninferior  
21 product for all populations is clearly described,  
22 clearly enforced, and robustly done.

1           So we do urge the committee to approve for  
2 all populations F/TAF for PrEP. We do urge the  
3 committee to consider the consequences of you  
4 voting no, which would send a signal of delay and  
5 distrust of the research community in a product  
6 development, and at the same time committing  
7 together that we are not changing the rules for  
8 future products of new PrEP agents, that we ensure  
9 that we have better conversations earlier in the  
10 process so the products coming to this committee  
11 and to the FDA are done with the most robust and  
12 complete package possible. Thank you very much.

13                           **Clarifying Questions (continued)**

14           DR. BADEN: Thank you.

15           Once again, the open public hearing speakers  
16 have presented us with incredibly powerful insights  
17 in the challenge at hand before us, and we thank  
18 all of the speakers for sharing your thoughts and  
19 convictions and insights in balancing this very  
20 difficult problem.

21           The open public hearing portion of this  
22 meeting is now concluded and we'll no longer take

1        comments from the audience. We'll now turn our  
2        attention back to the business at hand, which is  
3        evaluating the data presented before us, and we  
4        will continue with our clarifying activities with  
5        the applicant.

6                Prior to the applicant presenting some of  
7        the follow-up, I just had one clarifying question  
8        to the agency, which is adolescents, as I look at  
9        all the materials we've received, seems to be  
10       defined by a way to greater than or equal to 35  
11       kilograms, and that is not how I've always thought  
12       of adolescence. So I just want to know if there's  
13       an age parameter there or simply a weight  
14       parameter.

15                (Laughter.)

16                DR. BADEN: Is it 15 to 17 and of sufficient  
17       weight or is it down to 10, or down to 5? I just  
18       want to know are there any parameters around the  
19       adolescent category?

20                DR. MURRAY: I think we're sticking with  
21       weight. It becomes tricky to decide what age one  
22       should be starting to use.

1 DR. BADEN: So could it be 10 then?

2 DR. MURRAY: Well --

3 DR. BADEN: If it's purely weight, then I  
4 guess it could be a big 10 year old, could be 36  
5 kilos.

6 DR. MURRAY: We know the safety and how to  
7 dose down to 35 kilograms, and exactly when a  
8 physician or a person who's of adolescent age  
9 should consider it is probably up to them. And  
10 when you put an age in there, it kind of boxes you  
11 in, with a lot of respect.

12 DR. BADEN: Is Truvada 15? I thought  
13 Truvada was 15 to 17, or is that purely weight  
14 based? It's purely weight based.

15 DR. MURRAY: Weight based.

16 DR. BADEN: Okay. Well, thank you for  
17 the -- I just wanted to make sure I was reading  
18 weight as the determinant and not other factors.

19 So back to the applicant, who wanted to  
20 clarify some of the concepts from this morning that  
21 needed your input, and then we will come back to  
22 the many questions we have on the list from the

1 panel members.

2 DR. BRAINARD: Thank you. We have four  
3 clarifying answers to prior questions. The first  
4 is around the data for Descovy in vaginal tissue,  
5 and I'd like to just walk through what the  
6 available data are, so everyone has a clear  
7 understanding of the data in the literature.

8 Slide 1 up, please. There have been three  
9 different studies of Descovy in vaginal tissue.  
10 One was a single-dose study of Descovy, and in the  
11 discussion of that manuscript, they compared those  
12 results with another study that the same group had  
13 conducted several years prior with Truvada.

14 The second study was done with a single dose  
15 of Descovy and Truvada within the same study. The  
16 third study was done by the same group and was  
17 multiple doses of Descovy and Truvada looking at  
18 vaginal tissue levels.

19 Slide 2 up, please. Here are the results  
20 from those studies. In the first study, looking at  
21 Descovy vaginal tissue levels following a single  
22 dose of Descovy, the tissue levels of AUC was

1 reported as 132,098. This was compared in a  
2 cross-study comparison to the Truvada levels, which  
3 were noted to be 1.3 to 1.8-fold higher than those  
4 with Descovy.

5 The second study that was done with a single  
6 dose of Truvada or Descovy in the same trial  
7 demonstrated that after 4 hours, all of the samples  
8 with Truvada were below the limit of  
9 quantification, and 69 percent of the samples with  
10 Descovy were below the limit of quantification.  
11 The conclusion from that was that multiple dose  
12 data are needed.

13 In the setting of multiple doses, which is  
14 indeed the more relevant setting to assess tissue  
15 levels for a daily administered drug, 4 hours after  
16 dosing of Descovy or Truvada, levels were 2.6-fold  
17 higher with Descovy as compared to Truvada. FDA  
18 presented these data in their presentation. At 24  
19 hours and 48 hours after dosing stopped, there were  
20 comparable and low levels between Descovy and  
21 Truvada in the vaginal tissue.

22 I'd like to now put these vaginal tissue

1 data into context with what we know about the  
2 rectal tissue data. Slide 1 up, please. The  
3 vaginal tissue are just now a graphical  
4 representation of the data I showed you at the  
5 4-hour time point in the table, where you can see  
6 that Descovy achieves slightly higher levels than  
7 Truvada 4 hours after dosing.

8 As compared to rectal tissue levels, the  
9 first thing to note is that Truvada achieves about  
10 10-fold higher level than Descovy in the rectal  
11 tissue. It's also relevant to note that the rectal  
12 tissue levels with Truvada are somewhat of an  
13 outlier as compared to the vaginal tissue levels  
14 with both Descovy and Truvada, and the rectal  
15 tissue with Descovy.

16 This has been hypothesized to be related to  
17 the low bioavailability of Truvada, and the fact  
18 that there may be drug delivered directly through  
19 the GI tract to the rectal tissue with Truvada.  
20 That's done so to a lesser extent with Descovy,  
21 which has higher bioavailability. This is a  
22 hypothesis without clinical or scientific proof.

1           Nevertheless, what we know about Truvada is  
2           that despite the lower levels in the vaginal tissue  
3           as compared to the rectal tissue levels with  
4           Truvada, Truvada for PrEP is highly an equally  
5           efficacious in men and women. So these lower  
6           levels of vaginal tissue nevertheless correlate to  
7           having efficacy in the setting of Truvada for PrEP  
8           use in women.

9           Similarly, what we now know with the  
10          DISCOVER trial is that despite having 10-fold lower  
11          levels of tenofovir diphosphate in the rectal  
12          tissue as compared to Truvada, both drugs  
13          demonstrated that they were highly effective and  
14          Descovy was noninferior to Truvada at preventing  
15          HIV acquisition. These data contribute to the  
16          increasing body of understanding that systemic drug  
17          levels are what's driving efficacy, and efficacy is  
18          not related to particularly homogenate tissue  
19          levels.

20          I can keep going to the other issues or we  
21          can stop for comments, Dr Baden.

22          DR. BADEN: Thank you. Your point's well

1 taken. Since this is such an important issue,  
2 comments from the committee to better understand  
3 these data since these bridging data are a critical  
4 element.

5 DR. DODD: Lori Dodd, the statistician. One  
6 of the concerns I have looking at these data is  
7 they're extremely small numbers, and the box plots  
8 you're seeing are really the interquartile range as  
9 opposed to some confidence intervals. So I need  
10 some help understanding how generalizable these  
11 results are to the larger population. I'm unable  
12 to do that based on the data presented.

13 DR. BRAINARD: In terms of the  
14 generalizability, all tissue-level studies that  
15 have been conducted have generally been in less  
16 than 10 participants for group, occasionally  
17 somewhere between 10 and 15. This is just related  
18 to the invasive nature of conducting these studies  
19 and the requirements for a biopsy.

20 In addition, we haven't seen any data  
21 looking at tissue-level data in prevention studies  
22 because, of course, taking biopsies in the setting

1 of individuals who are at risk for HIV infection  
2 could actually increase their risk. So those data  
3 are not available, nor are they likely to be  
4 generated.

5 I would agree that the data are variable and  
6 that there are not a large amount of data.  
7 Nevertheless, when we think about what these data  
8 mean in the setting of a high amount of clinical  
9 data around the efficacy of Truvada for PrEP in  
10 both men and women, those data can provide  
11 reassurance.

12 DR. DODD: A little more clarity would help,  
13 too, then. How is it that states are coming up  
14 with guidelines on the amount of time needed to  
15 obtain maximum intracellular concentrations and  
16 pushing in that direction when we're only able to  
17 get 14 participants from this study? I might also  
18 ask if it would be appropriate to ask the agency to  
19 comment on this as well.

20 DR. BADEN: Yes.

21 DR. BRAINARD: During the lunch break, we  
22 tried to track down the data that actually were

1 behind the timeline recommendation around 20 days,  
2 and the data really come back to very sparse tissue  
3 data, and there are no data that connect to 20  
4 days.

5 One study showed that when assessing vaginal  
6 tissue levels and rectal tissue levels over time,  
7 it seemed that at the 10-day time period, there  
8 were stable and steady-state levels within the  
9 rectal tissue obtained with Truvada, whereas in the  
10 vaginal tissue, levels were still seen to be  
11 increasing. It seems like that is the basis for  
12 the extrapolation to 20 days required for  
13 prevention. But this has never been validated, and  
14 we don't know of any clinical data to speak to the  
15 time to protection for women.

16 DR. BADEN: Would you like the agency to  
17 comment if anyone is aware of the basis for those  
18 recommendations?

19 DR. DODD: And also if they can comment on  
20 their understanding of the uncertainty associated  
21 with the concentrations in the tissues given the  
22 small numbers.

1 DR. MIELE: Right. We actually have  
2 concerns about the reliability of that data because  
3 of the inconsistency and the small numbers, and the  
4 differences in methodology. But that's all we have  
5 right now, and the extrapolation approach is what's  
6 being proposed.

7 As to the time to achieve protection, I  
8 don't believe the CDC has a recommendation in that  
9 regard. What they're stating is the time to  
10 achieve maximum concentrations. Some state  
11 guidelines have interpreted that to mean protective  
12 levels, which kind of makes sense. But I agree  
13 that I don't know that the data are very robust to  
14 that extent, and these are very conservative  
15 measures.

16 We have not introduced any of that to the  
17 labeling, for example. We have not reviewed any of  
18 that data because as it stands right now, PrEP is  
19 meant to be used in combination with safer sex  
20 practices, so it's sort of counter-productive or  
21 counter-intuitive to suggest a lead-in period when  
22 you could come off condoms for example.

1           So we have not entertained that and we have  
2 not really reviewed that data, but I was pointing  
3 it out that that concern about the differential  
4 distribution is out there, and it's guiding some of  
5 these recommendations that are being put out there  
6 by states.

7           DR. BADEN: Do you have another follow-on,  
8 Dr. Dodd?

9           DR. DODD: Just one final comment, and I  
10 don't know if one of the statisticians who've  
11 looked at the concentration data could comment.  
12 But when I hear a number like a 10-fold increase in  
13 the tissue concentrations. That can tend to stick  
14 in everybody's mind, but we have to understand the  
15 uncertainty associated with that.

16           Has the confidence interval been estimated  
17 so that we don't get hung up on that number or  
18 something like that? I think this actually is a  
19 pretty important to point. I'll leave it at that,  
20 but I just want to make that as a final point.

21           DR. ZHENG: This is Jenny from FDA. The  
22 numbers we have for tissues normally were small

1 numbers and presented as median quartiles because a  
2 lot of below limit of quantitation was observed in  
3 those tissue concentrations, so there are some  
4 limitations.

5 DR. BADEN: Dr. Ofotokun?

6 DR. OFOTOKUN: Mine is just a minor  
7 clarification about the method. These tissue  
8 concentrations are generated in the rectal and the  
9 vagina. Can you confirm or clarify to me whether  
10 the vagina data, is it a biopsy of the vagina  
11 tissue, or is this CVL, or aspirate, or swab? How  
12 were they -- I know they are different sometimes  
13 when you look at those different compartments as  
14 opposed to rectal drug concentration.

15 DR. BRAINARD: There are a range of  
16 methodologies used for these compartments studies,  
17 and cervical vaginal lavage is often a method where  
18 tissue or cells are washed from the cervix, and  
19 sometimes with or without scraping. The data that  
20 I shared with you are biopsy data.

21 Slide 1 up, please. This slide provides a  
22 very high level schematic of how these tissue

1 levels are measured. Whether it's in the rectum or  
2 in the vagina, forceps are used to take biopsies.  
3 Generally with rectal tissue, more biopsies are  
4 taken than with vaginal sampling, where it's  
5 generally limited to 1 to 2.

6 These biopsies consist predominantly of  
7 epithelial cells and fibroblasts, which make up the  
8 majority of the tissue and point to some of the  
9 limitations of the sampling. Also contained within  
10 that biopsy will be a variety of immune cells,  
11 including relevant CD-4 T cells, but also  
12 macrophages, B cells, neutrophils, NK cells, and  
13 dendritic cells.

14 That tissue block is incubated with enzymes  
15 in order to break up the cells because the  
16 tenofovir diphosphate only exists inside cells. So  
17 it's released from the cells through enzymes, and  
18 then generally the amount of tenofovir diphosphate  
19 is quantified using mass spec. So the total  
20 tenofovir diphosphate level that is reported is the  
21 tenofovir diphosphate across all of these different  
22 cell types, recognizing that the predominant cells

1 that are contributing to these levels are  
2 epithelial cells and fibroblasts.

3 It's been hypothesized that part of the  
4 reason those vaginal tissue levels drop off at 24  
5 hours and 48 hours, and why there are so many BLQ  
6 measurements at those time periods is because  
7 epithelial cells have a more rapid turnover, and  
8 therefore tenofovir diphosphate within the  
9 epithelial cells, which are representing a higher  
10 proportion of contribution to the levels, are  
11 turning over and are no longer having tenofovir  
12 diphosphate at the 24-hour and 48-hour time point.  
13 That's just a hypothesis.

14 DR. BADEN: Thank you very much. Please  
15 continue with the other follow-ons from this  
16 morning.

17 DR. BRAINARD: Dr. Daskalakis asked about  
18 transgender women. There were 74 transgender women  
19 enrolled in the DISCOVER trial. None of those  
20 participants acquired HIV infection. There was  
21 also a question about gender-affirming hormone use,  
22 and 53 of the 74 transwomen reported using

1 gender-affirming hormones. We did look at the  
2 subset of those participants who had PK sampling  
3 down at the week 4 time point, and found that there  
4 was no difference in tenofovir diphosphate levels  
5 within that population.

6 Slide 2 up, please. This slide just shows  
7 data on the 18 women who were part of the substudy  
8 that had tenofovir diphosphate levels within PBMCs  
9 measured at week 4. And you can see that there  
10 trough concentration of tenofovir diphosphate is  
11 similar to what was seen in the MSM population,  
12 despite being on gender-affirming hormones.

13 DR. BADEN: Thank you. Any questions? I  
14 think these are fairly clear. Thank you.  
15 Continue.

16 DR. BRAINARD: The third issue was providing  
17 some additional information about insertive anal  
18 intercourse, and I'll ask Dr. Moupali Das to speak  
19 to that.

20 DR. DAS: Just to remind everyone, the  
21 eligibility criteria for the DISCOVER trial were in  
22 two parts. The first piece was requiring two

1 episodes of condomless anal sex with more than one  
2 unique partner in the past 12 weeks prior to  
3 enrollment, or the second criteria was evidence of  
4 rectal gonorrhea, rectal chlamydia or syphilis in  
5 the past six months, past 24 weeks. A high  
6 proportion of people in the study, as you saw,  
7 reported condomless anal sex.

8 We're going to share the data with you of  
9 the people reporting condomless insertive anal  
10 intercourse in terms of number of partners at  
11 screening prior to baseline. Slide 2 up. The mean  
12 number of insertive anal intercourse partners was  
13 4, which is the same as the report of condomless  
14 anal intercourse partners. There were no  
15 differences between arms. All the people who are  
16 infected in this study, the 22 people who acquired  
17 HIV, had data and biologic evidence of condomless  
18 anal intercourse.

19 DR. BADEN: Just to clarify, so I'm  
20 understanding these data and what's implied, do you  
21 have data on men who were insertive but not  
22 receptive? So purely insertive, and what degree of

1 transmission occurred in that population?

2 DR. BRAINARD: We don't have data on people  
3 who were purely insertive, but the criteria for  
4 eligibility in the study required evidence of  
5 receptive anal intercourse that was unprotected.  
6 There was no infections -- all the people who were  
7 infected had evidence of receptive anal  
8 intercourse.

9 DR. BADEN: Follow-on questions or  
10 clarifications for this?

11 (No response.)

12 DR. BADEN: Okay. Please continue.

13 DR. BRAINARD: The last topic I'd like to  
14 just proactively follow up is the question about  
15 study design issues in ciswomen. As has been  
16 pointed out by panelists, community members, and  
17 FDA, there are challenges with conducting a  
18 clinical trial in women, a superiority study for 2  
19 oral drugs that are tenofovir prodrugs as  
20 infeasible, and a placebo-controlled trial is not  
21 going to be ethical given Truvada is effective in  
22 women.

1           We talked a little bit about noninferiority  
2           and the challenges around establishing a  
3           noninferiority margin and FDA's perspective on the  
4           inability to construct a noninferiority margin  
5           because of the lack of consistency. We did look at  
6           taking the effect from the two most effective  
7           randomized clinical trials in women Partners PrEP,  
8           which was one of the registrational studies for  
9           Truvada, and then the Bangkok study, which was  
10          actually a study in injection drug users, but, most  
11          of the HIV acquisition in women was due to sexual  
12          transmission.

13                 So using the treatment effect from those two  
14          studies, we calculated a noninferiority margin  
15          using the same methodological approach we used for  
16          DISCOVER, and came up with a sample size of 22,000  
17          in a high-risk population. That would take 8 to 10  
18          years to conduct, which was part of the reason that  
19          we didn't initiate that study, particularly in the  
20          setting of the ongoing DISCOVER study.

21                 However, we also recognize there's been a  
22          lot of discussion since 2015 about this conundrum

1 of what can be done to assess the efficacy of PrEP  
2 in women, and also now where we are because of the  
3 DISCOVER results and because there's highly  
4 effective active comparator in Truvada, and now  
5 Descovy, going forward in men as well.

6 Dr. Murray from FDA has been one of the  
7 leaders in this area. We've been participating in  
8 discussions as well as with PrEP experts, and  
9 academics, and community members. There are some  
10 novel trial design methodologies that don't fall  
11 within the standard rubric, but I'm going to ask  
12 Dr. Wulfsohn to discuss some of those approaches  
13 from a statistical standpoint.

14 DR. WULFSOHN: Thank you. And just to  
15 clarify, the 22,000 that Diana referred to would be  
16 a study in Africa, so you're dealing with a high  
17 incidence rate of 4 per hundred person-years. In  
18 order to find the best noninferiority design, we  
19 also selected 2 of the 5 women studies which had  
20 the most benefit from Truvada. So we've cherry  
21 picked the two studies to try and help us reduce  
22 the sample size, and the lowest we can get it to is

1 22,000.

2 Now we're certainly open to more innovative  
3 ideas. And fortunately for us, Jeff Murray gave a  
4 great talk at IAS a week ago, and we're very  
5 receptive to some of the ideas that Jeff proposed,  
6 and I'd like to go through some of these in terms  
7 of how a woman's study could look. All of these  
8 are our proposals from Jeff, so I won't mention his  
9 name anymore.

10 It was proposed that there should be at  
11 least two placebo anchors in order to interpret a  
12 woman study. The two that come to mind would be,  
13 firstly, an epidemiologic assessment of the placebo  
14 incidence. We would envisage a study in Africa  
15 where that would be known based on current  
16 epidemiologic data, what the incidence is in women  
17 not on antiviral protection.

18 The second approach to estimate a placebo  
19 incidence could be based on the screening period  
20 from the study. Knowing how long it was from the  
21 last test to beginning treatment, that being the  
22 risk period, we could look at the subset of women

1 who are not on Truvada and assess the incidence.

2 And that would be a reference, placebo incidence.

3 The other thing that was proposed in order  
4 to assess whether a PrEP drug is effective is that  
5 it should lower the incidence by 5 to 10-fold. The  
6 idea came from oral contraceptives, where oral  
7 contraceptives actually lower the incidence about  
8 40-fold, but we're trying to be realistic.

9 Just for reference, if you look at the  
10 DISCOVER study where, granted, the adherence was  
11 very high, we're estimating that Truvada lowered  
12 the incidence by 10- to 20-fold based on two  
13 different ways of estimating the placebo incidence,  
14 and Descovy lowered the incidence by 20- to 40-  
15 fold. So these are both effective agents.

16 I'd like to bring up slide number 1, which  
17 is the noninferiority study we were talking about.  
18 But just with reference to these five studies, the  
19 two best studies, Partners PrEP and the Bangkok  
20 study, which had the lowest risk ratio, in Partners  
21 PrEP, we're lowering incidence 3-fold, and in  
22 Bangkok, we're lowering incidence 5-fold. These

1 are just the point estimates.

2 I would also add that in our own  
3 demonstration project where we've got a lot of  
4 real-world data in women, our estimate is that  
5 we're lowering incidence approximately 5-fold based  
6 on observing an incidence of 0.8 per hundred  
7 person-years, largely from cohorts in Africa where  
8 you'd expect of incidence of 4 per hundred  
9 person-years.

10 The 5-fold is as far as we are currently  
11 getting with current adherence rates. It's  
12 potentially possible to improve adherence and get  
13 greater effect sizes, but clearly the metric for  
14 what constitutes good enough efficacy will need to  
15 be tailored to the population and adherence that  
16 we're getting.

17 Another criteria, which is an extra  
18 criteria, not a different option, is that the  
19 incidence rate in the experimental arm should be no  
20 more than 0.5 higher than the active control, which  
21 would be Truvada, and that seems somewhat  
22 reasonable.

1           Another separate approach was proposed, and  
2           that is to look at the adherence subset of a study.  
3           So in DISCOVER, if you look at the individuals who  
4           are taking 2 or more tablets per week, we're only  
5           seeing 2 infections, one in each arm. So we are  
6           observing an incidence of less than 1 in a thousand  
7           in adherence subjects. And it was proposed that  
8           that threshold of 1 in a thousand is a reasonable  
9           measure of what constitutes an effective agent.

10           These are all good ideas and very innovative  
11           creative approaches that we can leverage and work  
12           with the FDA on to try and design a woman's study  
13           that answers the efficacy question, and we're  
14           committed to doing this.

15           DR. BADEN: Thank you. If FEM-PrEP and  
16           VOICE in the placebo groups had 5 per hundred  
17           person-years, I'm having trouble understanding how  
18           you come to a 22,000 person study, when if we look  
19           at the DISCOVER, which had a 1 per hundred  
20           person-years, you have a 5-fold increased event  
21           rate, yet a 3-fold increase in sample size? I'm  
22           having trouble understanding.

1 DR. WULFSOHN: Slide number 1 up. The main  
2 thing that's driving up the sample size is the  
3 weaker performance of Truvada in these women  
4 studies. In the design of DISCOVER, we estimated,  
5 based on the three historical controls, that we  
6 would lower incidence 5-fold. Here, when you pool  
7 these two best studies, you're lowering incidence  
8 3-fold. So it becomes a lot harder to retain 50  
9 percent of a weak effect.

10 DR. BADEN: I see your point. Still, I'm  
11 concerned with the assumptions, but I see your  
12 point.

13 Other questions? Please, Dr. Goetz?

14 DR. GOETZ: I want to come back to what you  
15 just said, the weaker performance of Truvada in  
16 these women. Are you stating that irrespective of  
17 adherence?

18 DR. WULFSOHN: No.

19 DR. GOETZ: And it comes back to Dr. Baden's  
20 question, then, as to why the sample size must be  
21 so large. Are you projecting that the women you  
22 will enroll will be non-adherent?

1 DR. WULFSOHN: Our interpretation of the  
2 data is that adherence is a primary driver of  
3 efficacy. As you've seen presented today, there  
4 are several thousand women who've been, uh, given  
5 PrEP and over a hundred thousand men who've been  
6 given PrEP. And if you look at the literature,  
7 there's a total of 6 case reports of individuals  
8 getting infected while on treatment.

9 So it's highly unusual to get infected while  
10 on adequate treatment or with adherence and that's  
11 why the threshold for what constitutes good enough  
12 is you need to have less than one in a thousand  
13 individuals getting infected, because that's what  
14 the current drugs can deliver.

15 DR. BADEN: Dr. Giordano?

16 DR. GIORDANO: But then, why did the  
17 DISCOVER study work?

18 (Laughter.)

19 DR. BADEN: It's a circular problem we're  
20 dealing with.

21 DR. GIORDANO: Because you expected a  
22 10-fold higher rate of HIV than you saw in both

1 arms. The adherence was extremely high, higher  
2 than was across the board in the previous studies,  
3 and yet you ended up with a noninferior drug,  
4 statistically proven noninferior drug in this  
5 population. I don't get it.

6 DR. WULFSOHN: My understanding is that if  
7 you're perfectly adherent to both Truvada or  
8 Descovy, there's no advantage to one or the other  
9 drug from an efficacy point of view. That's a  
10 hypothesis. In the data from Truvada, and similar  
11 for Descovy, we're seeing 1 and 2 and a half  
12 thousand approximately infections in individuals  
13 who are adherent; to find a DBS that's done every  
14 3 months, showing adequate drug levels.

15 On the other end of the spectrum, if you  
16 stop taking the drug completely, there's no  
17 difference between what the drug can provide you  
18 because it's not providing you any benefit. So the  
19 benefits, to the extent there is a benefit, is in  
20 the middle, the individuals who are not fully  
21 adherent but are taking some drug, and the PK  
22 properties of the drug lead us to believe that, at

1 least from the PBMC levels, that there could be an  
2 advantage to the efficacy with Descovy.

3 These data are somewhat suggestive, an  
4 unproven advantage. We don't have enough data to  
5 say even in that subset there's an advantage, and  
6 certainly the study overall hasn't shown  
7 superiority, but that's a hypothesis that can be  
8 tested in the future as well.

9 DR. BADEN: Dr. Walker, you had a question?

10 DR. WALKER: Yes, and it may not correlate  
11 to the discussion that's going on at hand. And  
12 forgive me if you have mentioned this. It's been a  
13 lot of information that's been presented here. But  
14 I just wanted to know, could you go back and let us  
15 know some information about these baseline  
16 demographics and exactly how the sites were  
17 selected? I'm just curious to know, especially  
18 within the U.S., knowing that HIV is not evenly  
19 distributed amongst states and regions.

20 So I'm just curious to know how your sites  
21 were selected, the 94 sites, and if you could just  
22 kind of give me some details on the states, rural,

1 urban, and if that led to the disproportion of  
2 African Americans in this study.

3 DR. BRAINARD: I'll ask Dr McCallister to  
4 come and describe our site selection process.  
5 While he's coming to the podium, I will say that  
6 the DISCOVER study enrolled 9 percent overall  
7 African American subjects. Within the U.S., that  
8 proportion was 13 percent. As I believe was  
9 pointed out earlier today, the population that we  
10 enrolled into DISCOVER was largely reflective of  
11 people taking PrEP today. It was not reflective of  
12 the people who are at highest risk for new  
13 infections right now.

14 Slide 2 up, please. This slide shows the  
15 percentage of blacks and Hispanic and Latino  
16 individuals enrolled in the DISCOVER trial on the  
17 left as compared to the percentage of blacks and  
18 Hispanic or Latino individuals taking PrEP today in  
19 the U.S. As you can see, our proportions were  
20 similar for DISCOVER for black participants, and we  
21 enriched somewhat for participants who  
22 self-identified as Hispanic or Latino.

1 I'll have Dr McCallister speak to the  
2 efforts we took to enroll a diverse range of sites  
3 in the study.

4 DR. McCALLISTER: We did specifically seek  
5 out sites that were in high background HIV  
6 incidence areas, in the U.S., Canada, and in  
7 Europe. In so doing, we went to -- almost all of  
8 them were urban centers, and they were in hospital,  
9 in STI clinics, and health departments.

10 Within the U.S. population that wound up in  
11 DISCOVER, we had a large percentage that were in  
12 the northeast and southeast in particular. One of  
13 the findings that has come out of our attempt to  
14 understand what the background epidemiology was of  
15 our sites, we used CDC data to get the HIV  
16 incidence rate in these sites, and then compared it  
17 to places where DISCOVER was conducted.

18 Could I get slide 1 up, please. These data  
19 are incidence rates over time at 25 metropolitan  
20 statistical areas inside the United States that  
21 overlapped with DISCOVER sites. These are  
22 incidence rates in MSMs in those locations who were

1 not using PrEP. What you see is over time, the  
2 general incidence rate in both the DISCOVER sites  
3 as well as non-DISCOVER sites has gone down a bit,  
4 but the DISCOVER sites were in places where the  
5 incidence was higher consistently over time.

6 DR. BADEN: Dr. Giordano, you had a follow-  
7 on?

8 DR. GIORDANO: Yes. Can you clarify if that  
9 comparison was adjusted for the racial and ethnic  
10 distribution of the participants matched for what  
11 the distribution is in the MSAs, weight sampling,  
12 in essence?

13 DR. McCALLISTER: Right. These data on the  
14 screen are all people at risk with a CDC indication  
15 within these MSAs. However, when you do break it  
16 down racially, the numbers are very close. They  
17 range from 3.3 to 4.2.

18 DR. GIORDANO: I'm not sure I understand  
19 that.

20 (Laughter.)

21 DR. GIORDANO: In other words, what I'm  
22 asking is does this comparison, where you're saying

1 these are high-risk people in high-risk areas, yes,  
2 they're in a high-risk area, but are they from a  
3 racial and ethnic group, that is at high risk in  
4 that area? So half of the HIV in Houston is in  
5 African Americans right now. If you only enrolled  
6 white people in Houston, you would get a lower rate  
7 of HIV incidence than you would otherwise expect.

8 Does this adjust for that difference?

9 DR. McCALLISTER: It doesn't adjust -- it is  
10 inclusive of all people in these MSAs.

11 DR. GIORDANO: So the answer is no.

12 DR. McCALLISTER: It's not adjusted --

13 DR. GIORDANO: Thank you.

14 DR. McCALLISTER: -- specifically just for  
15 African Americans; that's correct. The rate in  
16 African Americans and the rate in Caucasians from  
17 these locations are very close to these numbers.

18 DR. GIORDANO: Am I being obtuse? Is he  
19 being obtuse? We're not communicating.

20 DR. BADEN: The point has been made.

21 DR. GIORDANO: Okay. Thank you.

22 DR. BADEN: Dr. Le, did you have a

1 follow-on?

2 (Dr. Le gestures no.)

3 DR. BADEN: Okay. Dr. Goetz, a follow on?

4 DR. GOETZ: Yes. I'll try to follow up on  
5 what I think is Dr. Giordano's question. You had  
6 presented data on MSA, 1 metropolitan statistical  
7 area -- I believe that's what the MSA is -- would  
8 be Houston and another one would be Boston. The  
9 MSAs from which you recruited patients on average  
10 have higher rates of HIV acquisition than other  
11 MSAs.

12 But I think Dr. Giordano's question is, or  
13 my question is, the patients enrolled in the study,  
14 though, are they representative of the ratio makeup  
15 of that MSA, and thus it would be predicted to have  
16 that higher rate, or were patients who were  
17 enrolled in this study be from populations of lower  
18 risk, which gets back to the whole question of  
19 what's the risk of the population enrolled and  
20 thus, the efficacy of the intervention?

21 DR. BRAINARD: I think what your question is  
22 driving at is how confident can we be that we were

1 in the right population with high risk for HIV, and  
2 to address that, I'll ask Dr. Wulfsohn to come to  
3 the podium and speak to the two ways we tried to  
4 estimate the putative or potential placebo rate to  
5 understand whether we were in the right population.

6 DR. WULFSOHN: Just to answer the question  
7 directly, we did an analysis where we forced the  
8 racial makeup in the MSAs to match that in  
9 DISCOVER, and the rate went down by 0.3. It was  
10 3.8 overall in 2017, and 3.5 when you force it to  
11 match the racial makeup in DISCOVER. And we have  
12 looked at another method of assessing the placebo  
13 rate, and that's using the rectal gonorrhoeal  
14 approach, which I can show.

15 Slide 1 up. There have been 8 different  
16 cohorts within controlled trials of placebo  
17 control. Each of the 8 black dots on this graph  
18 represents a placebo cohort. What's notable is  
19 that the higher the rectal gonorrhoeal rate, the  
20 higher the HIV incidence rate in these placebo  
21 cohorts, and that's a linear relationship.

22 On this graph, we've also superimposed the

1 DISCOVER data, so just above 20 on the X-axis,  
2 you'll see 2 little dots, and these represent data  
3 from DISCOVER, gray for Truvada and blue for  
4 Descovy. For both arms, we have the erectile  
5 gonorrhoea incidence, as well as the HIV incidence.  
6 These 2 dots with the vertical confidence  
7 intervals, which are hard to see because they're so  
8 tight, are well below what the projected placebo  
9 incidence would have been, and that gray area is  
10 the 95 percent prediction interval around the  
11 placebo rate.

12 DR. BADEN: Dr. Smith, did you have a  
13 follow-on?

14 DR. SMITH: [Inaudible - off mic].

15 DR. BADEN: Microphone.

16 DR. SMITH: I had a question about the MSA  
17 slide.

18 DR. BRAINARD: We'll pull that up for you;  
19 just a sec.

20 Could we get the MSA slide, please?

21 DR. SMITH: Remind me the years in which the  
22 DISCOVER trial was actually happening, '16 to '17

1 or '15 to '17?

2 DR. WULFSOHN: It started at the end of '16,  
3 and it was largely in '17 as the bulk of the  
4 follow-up.

5 DR. SMITH: So the incidence was falling in  
6 both sets of communities before the start of the  
7 study, and you really only have the last two time  
8 points that are presumably related to the DISCOVER  
9 trial?

10 DR. WULFSOHN: That's correct. If I could  
11 have the slide on the fold increase relative to  
12 placebo from Truvada, with the MSAs? When we  
13 designed the study relative to the three historical  
14 studies that were used for the design, we expected  
15 Truvada to lower incidence 5-fold. So 1.44 was  
16 expected for Truvada versus 6.96 in placebo from  
17 the three studies.

18 Slide 1 up. When you look at the actual  
19 data from DISCOVER, we're noticing that Truvada is  
20 lowering the incidence by actually 8.6 fold if you  
21 were to use the MSA data; that's this middle CDC  
22 estimate of the placebo rate. The placebo rate we

1 estimated to be 3.83 during the duration of the  
2 study versus the USA subset of DISCOVER, where the  
3 observed Truvada incidence was 0.446.

4 Our active control was actually  
5 substantially more active than we anticipated.  
6 Using the rectal gonorrhoea, it's actually 19-fold  
7 reduction that we're seeing with our active  
8 control, Truvada. So DISCOVER was actually a  
9 better test of a new agent than we anticipated it  
10 to be.

11 DR. SMITH: Okay.

12 DR. BADEN: Dr. Dodd?

13 DR. DODD: Yes. Was it really a better test  
14 or was it just that the prevalence of circulating  
15 HIV in the populations tested might have been  
16 lower, and therefore exposure to HIV may have been  
17 lower? I think you made the case that their  
18 at-risk behavior was relatively high, but how do we  
19 know that the gonorrhoea curves that you showed and  
20 the really low rates in the DISCOVER cohort weren't  
21 just really because there was lower exposure to  
22 HIV?

1 DR. WULFSOHN: If I could have the  
2 gonorrhoeal slide back? If you look at the lower  
3 bound of the interval around the projected -- slide  
4 1 up. If you look at the lower bound of the  
5 interval around the HIV incidence that we projected  
6 for placebo, while we projected an incidence  
7 slightly above 6, the lower bound is slightly above  
8 3. So even in a conservative way of looking at  
9 this, there is a big gap between how placebo would  
10 have performed relative to how these two agents are  
11 performing.

12 DR. BADEN: Thank you. We're close to our  
13 break, but before we go to break, which I'll  
14 shorten to 10 minutes, one last question on  
15 ciswomen. Separate from this committee's  
16 deliberation and the agency's action, what is your  
17 commitment to studies in ciswomen in terms of  
18 generating the data that are absent?

19 DR. BRAINARD: We're firmly committed to  
20 generating data in women. As Moupali showed in her  
21 presentation, we've got a number of studies that  
22 we're supporting, that we're hoping to initiate

1 within the next year. These are not traditionally  
2 powered for efficacy studies; these are clinical  
3 effectiveness studies, and they are planned to be  
4 conducted both in the U.S. as well as in high  
5 incidence settings within Africa to demonstrate the  
6 safety as well as the clinical efficacy across a  
7 broad range of populations.

8 In addition, we are committed to generating  
9 clinical data with Descovy for PrEP in women using  
10 one of these novel approaches if we can come to an  
11 agreement on what that approach should be.

12 Dr. Wulfsohn walked through some of the ideas.  
13 We're in active discussions with investigators and  
14 with experts on how to best get this done, and  
15 we're committed to do it, and we're planning to  
16 incorporate the feedback that we receive from FDA  
17 and from the panelists into this decision.

18 DR. BADEN: So whether or not the indication  
19 is granted, you will conduct studies in ciswomen to  
20 determine the effectiveness.

21 DR. BRAINARD: Without a doubt.

22 DR. BADEN: And that's the hundred, in the

1       tens, hundreds, or thousands? I'm just looking for  
2       a zip code.

3               DR. BRAINARD: The indication allows us to  
4       go more broadly into clinical effectiveness  
5       demonstration projects, so it clearly allows us to  
6       get to a higher number and reach a higher number of  
7       women more quickly because we have endorsement from  
8       a regulatory agency that this drug is safe and  
9       effective in the population.

10              If we don't have an indication, we're still  
11       generating data in women, but the nature of that  
12       type of data has to be restricted until we get the  
13       endorsement from the regulatory bodies that we can  
14       then go and do these demonstration projects. So  
15       we're committed, we're going to generate data, and  
16       I think that the proportion and maybe the velocity  
17       of that data depends on where we land, but the  
18       commitment is there, and it will happen. The time  
19       period is it just depends.

20              DR. BADEN: Understood the constraints you  
21       have to work under.

22              It's 3:04. We will take a break and resume

1 at 3:15 sharp.

2 (Whereupon, at 3:04 p.m., a recess was  
3 taken.)

4 DR. BADEN: [Inaudible - mic off] -- before  
5 that, we need to clarify as much as we can from the  
6 applicant.

7 We have several committee members who still  
8 have questions from this morning. I will ask the  
9 committee members, as well as the applicant, to be  
10 as pointed as possible in the question and the  
11 response so that we can cover as much ground in the  
12 next 15-20 minutes before we have to get to  
13 discussion about the questions at hand.

14 I'm going to start with questions from this  
15 morning. Dr. Daskalakis, you are on the list.

16 (Dr. Daskalakis gestures no.)

17 DR. BADEN: Thank you. Dr. Green?

18 DR. GREEN: Yes. Thank you. I have a  
19 question that relates to the slide CC-50 from this  
20 morning, which was the forest plot looking at the  
21 different subgroups. I know there's been  
22 conversation. I thought that adolescence was part

1 of the populations that you were contemplating,  
2 including in your request for indication.

3 I wonder if you could explain, because the  
4 closest thing we have to adolescence is the age  
5 less than 25, and it's one of the only two data  
6 points on this curve that show a favoring to TBD,  
7 although not clinically significant, so maybe you  
8 could just comment on that.

9 DR. BRAINARD: Yes. I'll first make the  
10 point that there are wide confidence intervals  
11 around this point estimate related to the  
12 relatively small sample size as compared to the  
13 entire study design. The incidence rates within  
14 the population of participants who are less than 25  
15 are higher than the overall incidence rates.

16 This is related to the relationship between  
17 younger age and lower adherence, which has been  
18 demonstrated in many PrEP studies and certainly  
19 demonstrated in the adolescent ATN study with  
20 Truvada, and reflects that those participants had  
21 lower adherence in that age bracket. However, I  
22 would point out that both Descovy and Truvada

1           nevertheless were highly effective and  
2           substantially lowered the risk of HIV acquisition.

3           DR. BADEN: Thank you. A follow-on to that,  
4           safety in the younger ones, I have learned that  
5           adolescence is defined by weight of 35 kilograms.  
6           The data you have on how low an age bound, you have  
7           data. Do you have data on 10 year olds on Truvada,  
8           12 year olds, 20 year olds? I just want to have  
9           some sense of where we're are in the data-free zone  
10          if we may be giving it to our 10 year olds.

11          DR. BRAINARD: We have Truvada, Descovy, and  
12          then three other single-tablet regimens that  
13          contain Descovy, as well as multiple regimens  
14          containing Truvada, are indicated for adolescents  
15          greater than or equal to 35 kilograms. And then we  
16          also have indications in younger populations based  
17          on the data that we've generated in treatment  
18          trials.

19          So we have a fairly large body of evidence  
20          to suggest that the Descovy-based therapy is safe  
21          and well tolerated in these younger populations,  
22          even extending less than 35 kilograms.

1 DR. BADEN: When you say younger, is that  
2 from 0 to 10 years old in treatment?

3 DR. BRAINARD: In the setting of HIV  
4 treatment, our youngest -- I think our lowest  
5 weight indication is 25 kilograms.

6 DR. BADEN: Again, any labeling is going to  
7 need to take into consideration the absence of  
8 data.

9 DR. BRAINARD: I'm getting a signal that the  
10 age cutoff is 6 --

11 DR. BADEN: Six.

12 DR. BRAINARD: -- so down to age 6.

13 DR. BADEN: Okay. So you have safety data  
14 down to that obviously with indication.

15 Dr. Goetz, do you have a follow on?

16 DR. GOETZ: Not a follow-on.

17 DR. BADEN: So moving down, Dr. Gripshover,  
18 you have a question from this morning.

19 DR. GRIPSHOVER: Actually, yes. I had one  
20 question about weight, because we did see one slide  
21 from the audience earlier, too, especially in the  
22 HIV treatment world where being concerned with

1 obesity, they think some may be related to TAF,  
2 some also the ACE inhibitors. I think in this  
3 study they gained a kilogram in the men. It seems  
4 that sometimes women gain more weight.

5 So I just wondered if we have any data maybe  
6 in women on TAF outside of this if we're trying to  
7 extrapolate this to a broader population of women.

8 DR. BRAINARD: I'll ask Dr. Das to come in  
9 and discuss the weight gain in the DISCOVER study  
10 and place it into context around what we know from  
11 other PrEP trials. I'll also note that the data we  
12 have from our HIV treatment setting suggests that  
13 there are many factors associated with weight gain,  
14 integrase inhibitor therapy being one of them, and  
15 that's seen across different integrase inhibitors.

16 TAF in and of itself is not associated with  
17 weight gain. What we see in the HIV treatment  
18 space is that TDF is associated with a weight  
19 suppressive effect, and when TDF is switched to  
20 either a TAF-based regimen or a regimen without TAF  
21 that doesn't contain TDF, that can be associated  
22 with weight gain.

1 DR. DAS: The difference in weight in the  
2 DISCOVER study was driven by the TDF weight  
3 suppressive effect that Diana just discussed.  
4 Slide 2 up, please. We've known about the  
5 potential for Truvada to potentially suppress  
6 weight since the iPrEx trial. The USPI has weight  
7 loss as a known adverse drug reaction for Truvada,  
8 based on the iPrEx trial.

9 On the left-hand side, you see placebo  
10 across the top and Truvada across the bottom, and  
11 you see that with iPrEx, there was a weight loss  
12 through week 48 with Truvada and a weight gain on  
13 placebo. This is in median percent changes in  
14 weight. In DISCOVER, the Truvada arm looked very  
15 similar to the iPrEx arm with initial weight loss  
16 and a little bit of stabilization towards the end,  
17 and the Descovy arm looked very similar to the  
18 placebo.

19 The average placebo weight gain -- excuse  
20 me. The average amount an American age 18 to 40  
21 gains in a year is 1 kilogram, and the placebo  
22 weight gain in the iPrEx trial and the weight gain

1 in the DISCOVER trial on the Descovy arm are  
2 consistent with that. Further, if we look at  
3 HPTN 077, at 41 weeks, the placebo arm also gained  
4 about 1 kilogram. The cabo arm in that trial also  
5 gained 1.1 kilogram.

6 So I think what we're seeing in trials that  
7 compare TDF to TAF is the TDF weight suppression or  
8 stabilization effect versus the release of that  
9 effect in switch or the lack of that effect in the  
10 TAF arm.

11 DR. BADEN: Thank you. Dr. Le?

12 DR. LE: Can you please go back to slide  
13 CC-50 that you had earlier n in the subgroup  
14 analysis of those less than 25 years? You alluded  
15 to that this may have been where the incidence rate  
16 is a little bit higher than the overall -- was  
17 perhaps due to adherence as a reason for this.

18 What was the adherence for that group, and  
19 was it similar to the treatment trials that you see  
20 in adolescents? I'm trying to correlate this, for  
21 younger people would we see the same trends?

22 DR. BRAINARD: I'll ask Dr. McCallister to

1 address the issue of adherence by age within the  
2 DISCOVER trial, and I will say that, overall, we've  
3 seen lower levels of adherence within studies of  
4 PrEP in adolescents and younger individuals.

5 That was really one of the drivers for why  
6 we didn't include adolescence in the DISCOVER  
7 trial, was because of the data suggesting that they  
8 really benefit from an increased visit frequency.  
9 They're going to benefit from increased  
10 interventions to improve adherence and have age  
11 appropriate retention and recruitment methodology.

12 DR. McCALLISTER: Adherence in the  
13 individuals less than age 25 was lower than in  
14 those above age 25.

15 Could I get the slide 1 up please? This is  
16 the pill count data that is broken down by less  
17 than 25 years on the left, 25 to 50 in the middle,  
18 and above age 50 on the right. These are, as you  
19 can see, far lower for those less than age 25.

20 Another way of looking at it is through the  
21 dried blood spot data, so slide 3 up, please, and  
22 we really see the same pattern in the less than 25

1 using the TFV diphosphate levels in RBCs. There  
2 were fewer of them in a range of 4 tablets per week  
3 or higher. Of the 22 infections in DISCOVER, 7 of  
4 them did occur in this group, and all 7 of them did  
5 not have the detectable drug levels.

6 DR. BADEN: Thank you. Dr. Read from  
7 earlier in the day.

8 DR. READ: Yes, my questions have already  
9 been addressed. Thanks.

10 DR. BADEN: Dr. Giordano from earlier in the  
11 day.

12 DR. GIORDANO: I have a question for the  
13 agency. Is it within your -- two questions  
14 actually for the agency. One is, is it within your  
15 purview to say a registrational study should  
16 include X proportion of people in Y category? In  
17 other words, let's say a certain proportion are  
18 black, African American, from U.S.. Is that  
19 something you can say or is it really up to the  
20 sponsor to design that?

21 DR. BIRNKRANT: We can make the  
22 recommendation, but we wouldn't want to hold up a

1 trial or an approval if they didn't meet what the  
2 suggested rate would have been in that certain  
3 population.

4 DR. GIORDANO: Another question is, this  
5 request to approve based on essentially drug level  
6 extrapolation for women, do you have other examples  
7 of when the agency has allowed that to happen? Can  
8 you give us any guidance on when that's appropriate  
9 or considered inappropriate at the agency's level  
10 to help inform the committee?

11 DR. BIRNKRANT: I don't think we have any  
12 other examples, based on --

13 DR. MURRAY: The tissue level, we  
14 extrapolate efficacy for children all the time, and  
15 we still get the safety data. So we've matched  
16 efficacy in different populations based on systemic  
17 PK. I don't think we've ever made a regulatory  
18 approval decision based on a tissue a non-systemic  
19 PK argument.

20 DR. BADEN: And presumably the prior  
21 decision, you inferred the correlate of protection,  
22 so to speak, an antibiotic level in blood, where

1       there's an understanding of what the protective  
2       moiety supposedly is.

3               DR. MURRAY: We've always tried that, and  
4       we've tried to match it to be as much  
5       bioequivalent -- I use that term loosely -- to the  
6       population that had the clinical data.

7               DR. BADEN: Yes. Dr. Goetz?

8               DR. GOETZ: That leads me to what I think I  
9       can call a follow-up question. I want to go back  
10      to one of the backup slides that was shown, which  
11      showed correlation between dosage inferred from PBM  
12      of red blood cell spots and protection. I think  
13      that was BU461, is what I wrote down this morning,  
14      and that was in the iPrEx study.

15              What I was interested in is trying to build  
16      this bridge, which may or may not be buildable.  
17      Are there similar data that are inferred based on  
18      PBMCs or RBC studies in women that correlate the  
19      same level of protection to 2 to 3 tablets per week  
20      as being the cutpoint?

21              DR. BRAINARD: I'll ask Dr. Anderson to  
22      address this question about the thresholds for

1 adherence for women and for men.

2 DR. ANDERSON: I would say not this level  
3 and formal analysis in women. We just don't have  
4 that yet. We do have, though, the -- if I can show  
5 O82, perhaps. There's a very recent study  
6 HPTN 082; it was in women.

7 Slide 2 up, please. This study is one of  
8 the very few studies in women that have collected  
9 dried blood spots or a marker where you can tell  
10 different gradients of adherence, and this study  
11 did actually collect those. They had 4 infections  
12 in this study, and none of those infections  
13 occurred at the middle or the high drug, the DBS  
14 level. They all occurred at the low level.

15 DR. GOETZ: So aside from this sparse data  
16 set, there are no data at your disposal that allow  
17 us to map adherence -- a proxy for taking drug  
18 based on a biological measure that correlates, in  
19 some degree, with drug levels to protection in  
20 women, and shows equivalence between the level of  
21 protection that we expected in men with that level  
22 and the level of protection demonstrated in women,

1 because that's the bridge that we're trying to  
2 build, I think.

3 DR. ANDERSON: I think these results here on  
4 the screen are consistent with what we saw. And  
5 iPrEx OLE, it's a smaller data set, but it is  
6 consistent; I would say that. And I think you had  
7 something to add.

8 DR. GOETZ: Wide confidence interval.

9 DR. BRAINARD: I would also say that in the  
10 Partners PrEP study, there was an assessment of  
11 adherence based on tenofovir blood levels. And  
12 unlike tenofovir diphosphate within red blood  
13 cells, which is an integrated assessment of  
14 adherence over 6 to 8 weeks, tenofovir plasma  
15 levels reflect dosing within the last 4 days.

16 This is a measurement of adherence. It's  
17 less precise, but it does offer an objective  
18 assessment. And it is referenced in the new CDC  
19 guidance as a meaningful assessment of what they  
20 call recent PrEP use, which they correlate as  
21 associated with a 90 percent protection for both  
22 men and for women. Within that case-controlled

1 study, Partners PrEP, where they looked at both men  
2 and women who had detectable tenofovir diphosphate  
3 levels -- I'll put slide 3 up please -- the overall  
4 efficacy was 92 percent, and in men, it was 89  
5 percent, and in women, it was 94 percent.

6 So this represents a lower level of  
7 adherence than, for example, we saw in the DISCOVER  
8 trial. But nevertheless, it shows that there's no  
9 difference between men and women.

10 DR. BADEN: Thank you.

11 We've made it through the list. Are there  
12 other questions from the committee? We're not all  
13 satisfied given the nature of the data, but are  
14 there other questions that could help inform the  
15 committee in our deliberations?

16 (No response.)

17 **Questions to the Committee and Discussion**

18 DR. BADEN: If not, we'll now proceed  
19 with -- don't go yet to the questions to the  
20 committee, but thank you. We'll now proceed with  
21 the questions to the committee and panel  
22 discussions. I'd like to remind the public

1 observers, while this meeting is open for public  
2 observation, public attendees may not participate  
3 except at the specific request of the panel.

4 I would like to thank Dr. Brainard and the  
5 entire Gilead team for covering an incredible  
6 amount of information. Given the size of the  
7 problem, the amount of data could never approach  
8 the magnitude of the problem. We were able to get  
9 through I think about 15 percent of the slides you  
10 had prepared. If I'm reading the lower right-hand  
11 corner correctly, you have at least  
12 1500-1600 slides. I think we got 150 to 200 of  
13 them in front of us. So thank you for preparing  
14 the information and sharing it with us.

15 Now we must turn to the questions at hand.  
16 Before we move to the questions at hand, I have  
17 some guidance I would like from the agency, and if  
18 others have questions, let me know.

19 We're being asked -- and would be interested  
20 in the agency's guidance, too -- particularly in  
21 the cisgender women conundrum, I want to make sure  
22 I understand the problem correctly. There are

1 multiple studies with Truvada. At least two showed  
2 no benefit; two showed benefit. One of them led to  
3 the indication. However, these data were not  
4 strong enough to allow a determination of a study  
5 design with a noninferiority margin, yet these data  
6 are strong enough to guide us with a bridging study  
7 to lead to an indication.

8 Is that the position we're sort of in as  
9 we're reflecting on how to move forward with our  
10 deliberations?

11 DR. MURRAY: That's correct. Even though we  
12 had low efficacy in some studies, it was attributed  
13 to low or no adherence, but we think if women are  
14 adherent, that they should be 90 percent effective.

15 DR. BADEN: But that wasn't strong enough to  
16 set a noninferiority margin so you could have a  
17 female trial analogous to a male trial.

18 DR. MURRAY: Well, noninferiority studies  
19 are tricky; rely on historical data you're supposed  
20 to use as much as possible. I think the problem  
21 with noninferiority studies is you need that  
22 constancy assumption. You need to assume that what

1       you saw in the past is going to be repeated going  
2       forward, and for studies in Africa, we're not sure  
3       what the adherence rate is going to be, and then  
4       that really hampers our ability to do a  
5       noninferiority margin unless we did some novel way  
6       of looking at noninferiority margins, which we  
7       haven't done, Bayesian based on adherence and  
8       things that we've really never looked at.

9               DR. BADEN:  What tools do you have if broad  
10       indications were given to mandate or require future  
11       studies versus goodwill and intent to do future  
12       studies?

13              DR. MURRAY:  Well, obviously, I think this  
14       would be a postmarketing commitment.  Requirements  
15       are for pediatric studies and for safety.  This is  
16       really expanding indications, so it would fall  
17       under kind of a legal postmarketing commitment.  
18       But those studies, particularly in the HIV arena,  
19       are almost always completed, especially where  
20       they're important, like this would be, to expand  
21       the indication to women.

22              Anybody else want to comment on that?

1 (No response.)

2 DR. BADEN: Any other clarifying -- we have  
3 to deliberate -- sorry. Dr. Green?

4 DR. GREEN: So again, I'm going to be the  
5 pediatrician. On the packet that you have, it  
6 looks like the application -- again, it does  
7 include adolescents weighing at least 35 kilograms,  
8 but I noticed that neither question 1 nor  
9 question 2 addressed our opinion on adolescence.

10 So you're not interested in any opinions  
11 from the committee on adolescents?

12 DR. MURRAY: Yes, we were planning to ask  
13 that question. We were willing to extrapolate to  
14 adolescents based on what's known for PK and safety  
15 for the treatment and the fact that there's an  
16 indication in adolescence for Truvada. We're  
17 willing to kind of make that leap for the same  
18 gender in adolescence, because it's the route of  
19 transmission that we think could be the variable or  
20 acquisition.

21 DR. BADEN: Dr. Giordano?

22 DR. GIORDANO: Does an indication have to

1 specify sex or can it specify behavior? So  
2 approved for men who have sex with men or can it be  
3 approved for men -- but does it have to be approved  
4 for men? Do you see the distinction I'm making?  
5 Is that something within the labeling options?

6 DR. MURRAY: It is. Are you talking about  
7 MSM and heterosexual men, or those who have  
8 insertive intercourse with women, or men who have  
9 sex with men?

10 DR. GIORDANO: Before we get to that  
11 discussion, because there's no -- essentially --

12 DR. MURRAY: Yes. It gets a little bit  
13 tricky. But if the indication was limited just to  
14 MSM, we'd really have to think about how the  
15 indication would be worded for men in general.

16 DR. GIORDANO: Right.

17 DR. BADEN: Dr. Daskalakis?

18 DR. DASKALAKIS: Another labeling question.  
19 On a label, are you able to say that this drug has  
20 been studied in these populations; there's a  
21 recommendation for use in another population, but  
22 it's based on extrapolation? Is that something

1 that can be explicitly stated in the label?

2 DR. MURRAY: I think so. We do that, to a  
3 certain extent, when they describe pediatric data.

4 DR. BADEN: Dr. Smith, do you have a  
5 question?

6 DR. SMITH: Yes. Is it possible to discuss  
7 the MSM indication separate from the transgender  
8 women recommendation? Right now, they're in a  
9 single statement, and I think I have questions  
10 about one but not the others.

11 DR. MURRAY: Well, we didn't plan to have  
12 the question answered that way, but you might have  
13 that as a comment after your vote. But I think if  
14 we're prepared to go ahead with MSM, the agency was  
15 prepared to go ahead with the transgender women as  
16 well, realizing that you're not going to be able to  
17 do a powered study in transgendered women. There  
18 were zero seroconversions out of 74 probably  
19 indicative of some protection in and of itself in  
20 the DISCOVER trial.

21 DR. BADEN: But Dr. Smith, you're getting at  
22 just the power issue, given the population sizes.

1 DR. SMITH: Yes. I mean, if you look at the  
2 iPrEx subset analysis that had 200 transgender  
3 women defined slightly differently, there was no  
4 evidence of the impact, statistically significant  
5 evidence of protection.

6 So to me it's an extrapolation question. I  
7 mean, they didn't include enough transgender women  
8 in order to do a separate analysis, and now we're  
9 asking to make an indication based on the fact that  
10 it works for MSM. It was just my question.

11 DR. MURRAY: I think we're going to have it  
12 voted on as a package deal, and then you can  
13 explain why or why not you voted for it or not.  
14 And if that's one of the issues, you can explain  
15 that.

16 DR. BADEN: I think we'll vote on the  
17 questions as written, but I think your point is the  
18 guiding principle. We can then explain our  
19 concerns or our reinforcements of how we look at  
20 the different indications. After we vote, the  
21 agency finds our comments even more helpful than  
22 our vote. So it's very important that we'll vote,

1       which looks yes/no, but in reality, we can express  
2       different elements that we find reassuring or  
3       concerning where they should pay attention to.

4               I will be mindful of time, so we have about  
5       50 minutes, and we all have been very energetic,  
6       and it's a complex arena for all the reasons  
7       discussed earlier.

8               Any other discussion amongst the committee  
9       before we move to the vote? Are there any aspects  
10      of the data or what would charged with that it  
11      would be helpful to discuss or clarify?

12              (No response.)

13              DR. BADEN: If not, we can move to -- I can  
14      read -- we will be using an electronic voting  
15      system for this meeting. Once we begin the vote,  
16      the buttons will start flashing. It is a new  
17      system, so hopefully we won't get confused.

18              (Laughter.)

19              DR. BADEN: They'll continue to flash even  
20      after you have entered your vote. Please press the  
21      button firmly that corresponds to your vote. If  
22      you're unsure of your vote or you wish to change

1 your vote, you may press the corresponding button  
2 until the vote is closed.

3 After everyone has completed their vote, the  
4 vote will be locked in. The vote will then be  
5 displayed on the screen. The DFO will read the  
6 vote from the screen into the record. Next, we'll  
7 go around the room and each individual who voted  
8 will state their name and vote into the record.  
9 You can also state the reason why you voted as you  
10 did if you want to. We'll continue in the same  
11 manner until all the questions have been answered.

12 We will now move to the first question, and  
13 I will ask if there are any questions about the  
14 question before we vote. Has the applicant  
15 provided substantial evidence of the safety and  
16 effectiveness of Descovy for pre-exposure  
17 prophylaxis, PrEP, to reduce the risk of  
18 sexually-acquired HIV-1 infection in men and  
19 transgender women who have sex with men?

20 If yes, provide your rationale. If no,  
21 provide your rationale and list what additional  
22 trials are needed. Please provide any additional

1       comments or thoughts on your vote.  If yes, you can  
2       still have a rationale about studies that are  
3       needed.

4                So any questions about the question?

5                (No response.)

6                DR. BADEN:  If not, then let's proceed to  
7       voting.

8                (Voting.)

9                DR. BADEN:  I assume the voting from our  
10       online member is being handled.  Okay, so that is  
11       being handled.  So I'll wait until you close  
12       the --

13               DR. HOTAKI:  For the record, the vote is 16  
14       yes, two nos, zero abstentions, zero no votes.

15               DR. BADEN:  We will now go around the room  
16       and state your name and your vote into the record.  
17       And if you have comments to the agency, please  
18       share them.  We'll start with Dr. Goetz.

19               DR. GOETZ:  Thank you.  Matthew Goetz.  I  
20       voted yes, that the DISCOVER trial supports the  
21       approval of the Descovy, et cetera.  I think the  
22       word "support" is totally appropriate here because

1 it certainly supports the efficacy, and I use the  
2 word "efficacy" appropriately as well.

3 I think what is really needed to enhance  
4 this are the phase 4 trials to show the  
5 effectiveness in real-world populations that span  
6 transgender men -- I think I'm getting my  
7 phraseology right here or I mean to you -- and also  
8 in other populations and larger populations of  
9 African American men, and populations where all  
10 patients are to be fully adherent to PrEP.

11 The population that was tested here was  
12 gratefully a highly adherent population, and we saw  
13 a few infections. The real world I'm afraid  
14 includes individuals who are less adherent, and  
15 it's very important to demonstrate the  
16 effectiveness in other populations that may face  
17 challenges not seen in individuals who enrolled  
18 here. Certainly, you want to see long-term safety  
19 outcomes to see whether the biological signals that  
20 favor TAF lead to clinical outcomes that are  
21 favorable as well. I can go on, but I should leave  
22 my panelists to say more.

1 DR. BADEN: Dr. Smith?

2 DR. SMITH: I voted yes because I think  
3 there is substantial evidence to support an  
4 indication for men who have sex with men. I am not  
5 convinced that there's substantial evidence for  
6 transgender women, and I think that additional  
7 studies are going to be necessary, as my colleague  
8 said, to understand how this is actually used in  
9 populations that are at the highest risk of HIV  
10 acquisition and who stand to benefit from it.

11 Adolescents, black men and women, and  
12 transgender persons all have documented adherence  
13 problems with Truvada, generally, and I think it  
14 will be important to understand how TAF adds  
15 protection or not in those populations.

16 DR. BADEN: Thank you. Dr. Read?

17 DR. READ: I voted yes, and my comments  
18 largely have already been stated, but I think they  
19 bear repeating. I think the data provided by the  
20 applicant do support the safety and efficacy of  
21 Descovy by demonstrating noninferiority to Truvada  
22 in men who have sex with men and transgender women.

1 I think although there were a few infections  
2 in the trial, the high rates of STI infections and  
3 other indicators do support the high risk  
4 characterization of the study population. And  
5 further, Descovy appears to be safe as demonstrated  
6 both in DISCOVER as well as the extensive treatment  
7 experience in people living with HIV.

8 I do think that it has been stated  
9 throughout the course of the day that the study  
10 population enrolled in DISCOVER did not represent  
11 the populations most at risk for HIV, and  
12 therefore, if Descovy is approved for use in MSM  
13 and transgender women, the applicant should be  
14 required to collect postmarketing data on safety  
15 and effectiveness in those underrepresented  
16 populations, including transgender women, as has  
17 just been stated, as well as people of color.

18 I think it's important, as was raised during  
19 the public comment period, that the labeling and  
20 advertising for Descovy, if approved, should only  
21 speak to the noninferiority, not the superiority of  
22 both the effectiveness as well as the safety of

1 Descovy. I think it's important to note that the  
2 markers for kidney and bone toxicity were  
3 biomarkers only and did not indicate a clinical  
4 benefit. And I also think that it's important not  
5 to disregard some of the potential negative adverse  
6 events, including weight gain and lipids.

7 DR. DASKALAKIS: I'm Demetre Daskalakis. I  
8 also voted yes. Mirroring some of the prior  
9 comments, I think that the data presented in the  
10 DISCOVER trial are very strong for supporting the  
11 noninferiority of Descovy for pre-exposure  
12 prophylaxis in men who have sex with men. I do  
13 want to state again the importance of selling this  
14 as a noninferiority both from efficacy and safety.

15 I think overselling the safety here could  
16 create an environment where drug switches are done  
17 in a way that don't reflect the data and may also  
18 create significant disparities in various  
19 populations of men who have sex with men.

20 My expectation of this approval is that it  
21 should be marketed responsibly from the perspective  
22 of not creating these disparities and having

1 Truvada be a drug for poor people and Descovy be a  
2 drug for rich people, or for insured versus  
3 uninsured. So I think it's really important that  
4 we don't oversell the elements of noninferiority.

5 From the perspective of transgender  
6 individuals, and I'm including transwomen and  
7 transmen who have sex men on that list, I think  
8 more data are necessary. I think that in the same  
9 breath that we're going to probably discuss women,  
10 we should also discuss transwomen and transmen and  
11 the need and responsibility to actually get more  
12 robust data.

13 Historically, the answer it's hard to do has  
14 created a lot of disparity and mistrust of both  
15 public health and research among transgender  
16 individuals, so we need to work with strategies to  
17 go beyond that rather than to stay with that.

18 Ultimately, then I think with the caveat of work to  
19 do in the transgender population, I stand by my  
20 vote of yes for noninferiority men who have sex  
21 with men.

22 DR. GIORDANO: Tom Giordano. I voted yes

1 largely for the reasons that have already been  
2 stated. I agree completely with the comments  
3 already made. I will comment that I am not  
4 convinced that we have enough data to say anything  
5 about transgender women.

6           However, I did vote yes on that, including  
7 that language, mainly because the biological  
8 similarities is anal receptive sex primarily is the  
9 risk factor. So I agree that there's sufficient  
10 evidence, that that population probably would be  
11 protected with this noninferior drug.

12           DR. DODD: Lori Dodd, and I voted no because  
13 the question had the term "men and transgender  
14 women," so my concern is really related to  
15 transgender women. I agree with the comments said  
16 previously, so I won't articulate further.

17           DR. BADEN: Dr. Walker?

18           DR. WALKER: Dr. Walker here. I voted no  
19 for all the reasons that were expressed. According  
20 to the CDC, more than 290,000 African Americans  
21 with stage 3 HIV have died since the inception of  
22 the HIV epidemic. As African Americans remain

1 disproportionately at risk for HIV, with gay and  
2 bisexual men and heterosexual women being affected  
3 more than any other race ethnicity, there was not  
4 substantial or compelling evidence to indicate the  
5 safety and effectiveness of Descovy for PrEP to  
6 reduce HIV infection among this population. So  
7 that's why I voted no.

8 As a public health researcher and a  
9 community advocate, and an African American  
10 heterosexual woman, I have alarming concerns  
11 regarding the safety of Descovy, as well as the  
12 sexual behaviors that will result from individuals  
13 taking this drug. There was a lost opportunity to  
14 provide data, substantial data, that is reflective  
15 of the community in which its greatly impacted by  
16 HIV. Furthermore, the data from the DISCOVER trial  
17 failed to enough data on the prevention of HIV in  
18 cisgendered women.

19 DR. BADEN: Thank you. Dr. Le?

20 DR. LE: I voted yes for this, for the  
21 reason that the drug combination has demonstrated  
22 noninferiority to Truvada and offers an alternative

1 for PrEP, which is critical in light of data  
2 showing that only 7 percent of CDC's estimate of  
3 1.1 million people in the United States with PrEP  
4 indication actually received PrEP. Also, Descovy  
5 may offer potential advantages of reduced bone and  
6 renal toxicity. Despite voting yes, I do agree  
7 that we need more information on transgendered  
8 women.

9 DR. BADEN: Thank you. Dr. Burgess?

10 DR. BURGESS: Tim Burgess. I voted yes. I  
11 think that data from the DISCOVER trial met the  
12 noninferiority to Truvada, and just that, in men  
13 who have sex with men.

14 DR. BADEN: Dr. Ofotokun?

15 DR. OFOTOKUN: Igho Ofotokun. I voted yes  
16 for the same reasons that have been expressed by my  
17 fellow committee members. I am convinced that  
18 Descovy is noninferior to Truvada, and I think it  
19 should be emphasized that this is a noninferiority  
20 study.

21 Even though I voted yes, I am particularly  
22 very concerned about the low number of non-white

1 participants in this study, and that should be  
2 noted. I think if this moves forward, the agency  
3 should strongly recommend a postmarketing study  
4 that really include all this population, especially  
5 men who have sex with men, black men who have sex  
6 with men, who are most affected by this epidemic in  
7 the U.S.

8           Again, I think, as has been expressed,  
9 there's not enough transgender women to be able to  
10 make a strong recommendation, but I believe, based  
11 on the data, that it will be effective. And again,  
12 this is another population that should be studied  
13 should this approval move forward.

14           I think we should also emphasize the side  
15 effects related to Descovy. It's sold as a safer  
16 drug. I may be safer in some aspects, but there  
17 are other aspects. For instance, the lipid profile  
18 of Descovy is definitely something that should be  
19 emphasized, and I am still concerned that the jury  
20 is not yet out on the weight gain issue with TAF.

21 Thank you.

22           DR. BADEN: Thank you.

1           Lindsey Baden. I voted yes. We'll just  
2 highlight some key issues. The continuum of the  
3 body of evidence from the prior studies with  
4 Truvada, with DISCOVER, it's a continuous set of  
5 data that work well together and are very  
6 reassuring that in MSM, it works very well.

7           I share the concerns in the population  
8 studied, that's where we have the data.  
9 Transgender were a very small subset, and then  
10 other ethnic and racial backgrounds also have  
11 limited representation, so that will just have to  
12 be part of the consideration to grow the data set.

13           I think the weight and the lipids are not  
14 trivial issues and can become significant over  
15 years of treatment and perhaps consequence or not,  
16 but that's where data and follow up will be  
17 required.

18           Dr. Weina?

19           DR. WEINA: Peter Weina. I voted yes. I  
20 believe there is substantial evidence of the safety  
21 and effectiveness to reduce the risk of  
22 sexually-acquired HIV in the indicated population.

1 Ignoring all the background politics, potential  
2 gamesmanship, market pressures, whatever, this is  
3 another approved product in our toolbox that gives  
4 clinicians an option that we didn't previously  
5 have.

6 While no package is ever ideal for all  
7 potential patient populations, it actually was nice  
8 to see a trial that was reasonably powered given  
9 the targeted population, and in time when even more  
10 is known about it, available to all patient  
11 populations.

12 DR. BADEN: Dr. Green?

13 DR. GREEN: Michael Green. I voted yes. I  
14 thought the data as presented clearly met the  
15 criteria for noninferiority and have an equivalent,  
16 if not superior, safety profile, though the impact  
17 on lipid metabolism and weight gain might balance  
18 out the bone density and renal benefits if they are  
19 real. With the caveat that the study did not  
20 include enough transgender women to allow subset  
21 analysis, the study was generally well designed,  
22 including a large cohort and robust follow-up.

1           If approved, the label should clearly  
2 highlight the noninferiority performance of F/TAF  
3 and not infer superiority. Safety claims should  
4 highlight not only the potential benefits in terms  
5 of renal and bone density but also the potential  
6 increased risk related to lipid metabolism and  
7 weight gain and obesity. Thank you.

8           DR. BADEN: Thank you. Not yet,  
9 Dr. Gripshover. We have Dr. Lupole on the phone.  
10 Do you have?

11           MS. LUPOLE: [Inaudible - distortion]

12           DR. BADEN: We're having trouble hearing  
13 you. Now we can hear you.

14           MS. LUPOLE: All right. Can you hear me  
15 now? [Inaudible - distortion].

16           DR. BADEN: That may not be working well.  
17 Mute your computer while you speak is the advice  
18 I'm given.

19           MS. LUPOLE: I'm sorry. What, sir?

20           DR. BADEN: That sounds good. What you just  
21 did worked.

22           MS. LUPOLE: Okay, good. I voted yes. I

1 have concerns for transgender. I think more data  
2 needs to be collected, but yes is the answer to the  
3 question the way it was presented.

4 DR. BADEN: Thank you. Dr. Gripshover?

5 DR. GRIPSHOVER: I also voted yes. I  
6 believe the DISCOVER trial showed the efficacy and  
7 safety of Descovy to reduce the risk of HIV  
8 acquisition in men. I think it's a little bit of a  
9 stretch for transgender women, but I also agree  
10 it's the same biologic, at least method, of  
11 acquisition. But I think a small amount, but  
12 statistically significant improvements in bone  
13 mineral density and renal tubular function in TAF  
14 versus TDF may be important in young adults  
15 building bone and older ones losing it, or those  
16 with other comorbidities and renal function.

17 However, for the vast majority of people,  
18 TDF/FTC is safe, and I would not want those without  
19 access to TAF due to geography or cost to forego  
20 its benefit as PrEP, and I think we need to  
21 emphasize that this was a noninferiority study.

22 DR. BADEN: Dr. Siberry?

1 DR. SIBERRY: George Siberry. I voted yes.  
2 Like many before me, I think the trial adequately  
3 provided evidence for a claim for noninferiority as  
4 an alternative, both from an efficacy and a safe  
5 clinically meaningful safety standpoint. I'd add  
6 that the claim would include adolescence. I  
7 strongly support the use of weight without age down  
8 to 35 kilos and accept the ability to extrapolate  
9 for adolescents in that claim. Thank you.

10 DR. BADEN: Dr. Swaminathan?

11 DR. SWAMINATHAN: Yes. I agree that there  
12 was evidence of noninferiority as far as the  
13 efficacy in MSM, but that the numbers were  
14 insufficient to draw a clear conclusion about  
15 transgender women.

16 Nevertheless, because I think the number of  
17 variables that would have to be controlled for the  
18 number of patients that would have been required to  
19 be enrolled wouldn't really been feasible, and I  
20 agree that it may have to depend on postmarketing  
21 evaluations. But the way the question was phrased,  
22 I agree that they did provide substantial evidence

1 of efficacy.

2 DR. BADEN: Dr. Cheever?

3 DR. CHEEVER: Laura Cheever. I voted yes,  
4 and I think there is adequate evidence through the  
5 DISCOVER trial for noninferiority. I am disturbed  
6 that this far into the epidemic and this many  
7 clinical trials, we still can't do trials in the  
8 people most at risk in this country,  
9 representatively, and that we really do need to be  
10 looking at African Americans.

11 I echo other people talking about the lack  
12 of transgender women really represented in this  
13 trial. Once again, that needs to be looked at to  
14 better understand the efficacy or noninferiority in  
15 that population.

16 DR. BADEN: Thank you.

17 For question 1, it was 16 to 2, but even  
18 those who voted no, there was a large consensus in  
19 viewpoint that the data do support efficacy.  
20 However, it's in the population studied, and there  
21 was limited power in transgender and other key  
22 populations, as well as some safety signal in

1 weight and lipids.

2 Those will all have to be carefully followed  
3 and monitored in a postmarketing setting. The  
4 database expanded in the key at-risk populations,  
5 especially the transgender, and it's a  
6 noninferiority, not superiority, on either of the  
7 key issues.

8 Now we can move to question 2. Do the data  
9 from the DISCOVER trial, in combination with the  
10 available pharmacokinetic data and other previous  
11 HIV-1 prevention trials with Truvada in cisgender  
12 women, allow for the expansion of the DISCOVER PrEP  
13 indication to include cisgender women?

14 If yes, please provide your rationale. If  
15 no, please provide your rationale and list what  
16 additional studies/trials are needed. Also comment  
17 on the trial designs that would be adequate to  
18 expand the indication. Please provide any  
19 additional comments or thoughts on your vote.

20 Any questions about the question?

21 Dr. Siberry?

22 DR. SIBERRY: It's not simply asking whether

1 we would support expanding the indication, but  
2 specifically saying do we think that the data are  
3 the reason that we would expand it? Am I reading  
4 that right? Because it's a little nuance there, I  
5 think.

6 DR. BADEN: My read of this -- and the  
7 agency can please correct me -- is do we believe  
8 there are data establishing substantial efficacy  
9 and safety in this population, which is cisgender  
10 women, given the totality of the information  
11 provided.

12 Is that the intent of the question?

13 DR. MURRAY: Yes.

14 DR. BADEN: Does that answer your question?

15 DR. SIBERRY: Yes.

16 DR. BADEN: If no other questions, then  
17 let's vote.

18 (Voting.)

19 DR. HOTAKI: The online voter is being  
20 handled; all done.

21 One more person needs to vote, so if  
22 everyone can press theirs again.

1 DR. BADEN: Everyone repress your button.

2 (Pause.)

3 DR. HOTAKI: For the record, the vote is 8  
4 yes, 10 no, zero abstention, zero no voting.

5 DR. BADEN: Please state your name and your  
6 vote into the record. We'll start with  
7 Dr. Cheever.

8 DR. CHEEVER: Laura Cheever. I voted no. I  
9 really think that the company's demonstrated  
10 difference in metabolism in TDF and TAF, and we  
11 really do not know the protective factors for PrEP,  
12 exactly how it works in the mechanisms. I know  
13 that we do know that we have differences in  
14 immunologic milieu between the vagina and the  
15 rectal mucosa, so I have real concerns there about  
16 what has been shown.

17 That said, I wanted to vote yes because the  
18 thought of not having this indicated for women I  
19 think will only further inhibit the implementation  
20 of PrEP among women. So from a public health  
21 perspective, I think there's probably more harm  
22 than good not approving it for this indication, but

1 that wasn't the question that was asked.

2 So that's sort of how I split that. We've  
3 talked about it all day long. The failure to  
4 implement PrEP in women is huge. We keep glossing  
5 over it and trying to just get to the adherent  
6 women and throwing out all the rest, and I think  
7 that is the wrong conversation to be having.

8 It's really about why women and why  
9 transgender persons in youth and what we can do to  
10 better get them to have protective effects of PrEP,  
11 and whether that's different modalities or whatever  
12 is part of that larger discussion that we weren't  
13 having today.

14 DR. BADEN: Dr. Swaminathan?

15 DR. SWAMINATHAN: I voted no because -- I'll  
16 just go through the reasons here. I think as far  
17 as the question as to what the data allowed you to  
18 conclude is what's key here. The cells that are  
19 being infected in the vagina and cervix versus  
20 those in the rectal or penile mucosa are not  
21 clearly defined.

22 So although virus transcytosed in the

1 mucosal epithelium must infect dendritic or CD-4  
2 cells resident in all tissues, the resident target  
3 cell population at the time of exposure is the  
4 local pool of T lymphocytes. This pool is known to  
5 be relatively static, and more so in vaginal  
6 tissues than in the GI tract. They are also  
7 long-lived and replenished by local expansion.

8           Thus, the PK and PD in these lymphocytes may  
9 not be the same as those in the peripheral blood or  
10 other anatomic sites. We just do not know. Thus,  
11 the relative efficacy of TAF and TDF may differ  
12 between rectal and vaginal tissues and between MSM  
13 and cisgender women.

14           Measurements of tissue drug levels in this  
15 context is not particularly relevant. As unlike  
16 with PBMCs, the levels are not being measured  
17 primarily in cells that are infected but by rather  
18 in bulk populations of extremely heterogeneous  
19 cells from biopsies. And while there's evidence  
20 that the safety profile of TAF may be superior,  
21 particularly for long-term use, this has to be  
22 balanced against the possibility of inferior

1 efficacy.

2           In this situation, a relative lack of  
3 efficacy may translate into a currently incurable  
4 infection. Thus, one has a potential choice  
5 between long-term morbidity versus immediate risk.  
6 Nevertheless, I do not believe that we can state  
7 with scientific validity that TAF/FTC is as  
8 effective as TDF/FTC in cisgender women for PrEP.  
9 Extrapolation from one group to another is  
10 defensible if there is no scientific reason to  
11 believe that there could be pharmacokinetic or  
12 pharmacodynamic differences between the two groups.

13           That is not the case here, and therefore the  
14 basis for extrapolation from TDF to TAF in  
15 cisgender women is not obvious. The absence of  
16 actual clinical data in this group combined with  
17 the potential difference in the site of exposure,  
18 and other potential gender-based biological  
19 co-factors, do not allow me to recommend labeling  
20 this drug as effective in cisgender women.

21           I do not believe the drug should be approved  
22 or labeled without adequate evidence merely because

1 doing the necessary clinical studies would be  
2 challenging. The alternative is to potentially  
3 expose segments of the population who are  
4 underrepresented in studies to ineffective therapy.

5 DR. BADEN: Dr. Siberry?

6 DR. SIBERRY: George Siberry. I voted no.  
7 I think that there's good evidence of a biologic  
8 correlate of adherence. I remain unconvinced that  
9 we have a good biologic correlate for protection.  
10 For the reasons Dr. Swaminathan said, I think it is  
11 inappropriate to extrapolate to women. However, I  
12 feel like we have failed women by letting this  
13 application come in without data from women to  
14 begin with, and I fear we're failing them again by  
15 having approval for use in men and not women.

16 That's why I asked for that clarifying  
17 question about the question because I think these  
18 are two different things, and I would be supportive  
19 of an indication that includes women with a strong  
20 postmarketing requirement for clinical evaluation  
21 in women. Thank you.

22 DR. BADEN: Dr. Gripshover?

1 DR. GRIPSHOVER: Hi. Barb Gripshover. I  
2 also voted no. I do not believe the data support  
3 TAF/FTC efficacy as PrEP for women, as it's not  
4 been studied in that population, and I don't think  
5 it's clear that just the level of tenofovir  
6 diphosphate in PBMCs is the sole determinant of  
7 efficacy in women at risk for cervical vaginal  
8 infections or the reasons the gentlemen have just  
9 said.

10 I believe there is a large unmet need of  
11 women at risk of acquiring HIV worldwide that  
12 should be able to engaged in studies to answer this  
13 question; maybe using matched geographic  
14 demographic incidence rates as a control or  
15 incidence in screening that has been suggested.

16 While I do not like the idea of approving a  
17 drug for a single population, as it does look  
18 effective in MSM, I also think we are obligated to  
19 base our recommendations for use of a drug based on  
20 data. Women in underserved populations deserve our  
21 best efforts to make sure drugs are effective and  
22 safe for them as well before we start recommending

1 it in lieu of one that has demonstrated safety and  
2 efficacy.

3 So if the drug is approved for MSM, then I  
4 would absolutely require a strict efficacy setting  
5 in women as part of the agreement.

6 DR. BADEN: Wait, Dr. Green. Dr. Lupole?

7 (No response.)

8 DR. BADEN: You're on mute if you are  
9 talking.

10 (No response.)

11 DR. BADEN: Okay. We may have lost the  
12 connection. We can try to bring Dr. Lupole on.

13 MS. LUPOLE: Can you hear me now?

14 DR. BADEN: We can hear you now.

15 MS. LUPOLE: Okay. Sorry about all this.

16 I voted no as well. The lack of data, the  
17 lack of study participants, conflicting data, it's  
18 my recommendation that the trial for this drug in  
19 cisgender women and juveniles be redesigned to  
20 examine the impact because it's clear it's not been  
21 presented to me that it would be safe and  
22 effective. Thank you.

1 DR. BADEN: Thank you. Dr. Green?

2 DR. GREEN: Michael Green. I voted yes, but  
3 I almost abstained and I almost voted no.

4 (Laughter.)

5 DR. GREEN: With regards to extension of  
6 approval to cisgender women, the key concern of the  
7 FDA appeared to have been relating to the tissue  
8 level in vagina and cervix, and that those  
9 associated with TAF were lower than TDF.  
10 Therefore, the absence of a trial in cisgender  
11 females directly to confirm efficacy, they're  
12 asking us if we can extrapolate to extend approval  
13 based on the DISCOVER population.

14 However, the data that was presented suggest  
15 that TDF also has low levels, both at 4 four hours,  
16 and at 24 hours, and 48 hours, and yet F/TDF  
17 carries an approval in men, women, and adolescents  
18 for pre-exposure prophylaxis against HIV and is  
19 considered effective in these populations if those  
20 taking it are compliant.

21 Accordingly, it's not clear that low tissue  
22 levels had any impact on the effectiveness of

1 Truvada, and it seems unlikely, at least to me,  
2 that it would for Descovy. Clearly, there is not a  
3 concern that intracellular levels in PBMCs would be  
4 different between men and women. We've also heard  
5 the agency state that they feel challenged by  
6 developing design for noninferiority studies, and  
7 that there's no reason to expect a positive outcome  
8 in a superiority trial, and that a comparison to  
9 placebo would be unethical.

10           Given these issues, I felt it was  
11 appropriate to include cisgender women in the  
12 indication, especially given the equity issues that  
13 have been discussed during this committee hearing.  
14 Having said that, it would be important to mandate  
15 postmarketing studies and this indication be  
16 undertaken by the sponsor. And if these subsequent  
17 studies did not bear out efficacy in cisgender  
18 women, that the label be modified to reflect this  
19 if not having the indication removed. Thank you.

20           DR. BADEN: Dr. Weina?

21           DR. WEINA: Peter Weina. I voted yes, but  
22 the answer is really maybe. The reality is that we

1 really don't have a clue which is the appropriate  
2 surrogate marker to use. Is it the tissue level?  
3 Is it potentially PBMC levels? Is it adherence  
4 that's the key? Or is it more likely something we  
5 haven't even considered yet because we haven't  
6 bothered to count it, and some revelation years  
7 from now is finally going to give us that insight?

8 Right now, it seems like the surrogate  
9 marker selected depends upon which opinion you'd  
10 like to have supported, and the science behind it  
11 is whichever you select, and that seems very  
12 whimsical. So I reach back to the FDA's mission  
13 statement, and the mission statement is to promote  
14 and protect the public health by helping safe and  
15 effective products reach the market in a timely  
16 manner and monitor the products for continued  
17 safety after they are in use.

18 This product is already out there for  
19 treatment. It's already being demanded by patients  
20 who are subjected to social media pressures, and  
21 this is only going to accelerate. I have  
22 absolutely no doubt that this is already being used

1 in cisgender women somewhere here in the United  
2 States, and it's not being followed.

3 We should follow the FDA's mission statement  
4 to get this to the market for the broadest  
5 population possible and reasonable, and then  
6 monitor the product for continued safety. Here of  
7 course, I'm referring also to the efficacy because  
8 if it doesn't work, then it's putting the users at  
9 risk.

10 If approved for MSM and transgender women,  
11 it's definitely going to be used either off label  
12 or on label in adolescents and in cisgender women  
13 just because of the perception of better safety.  
14 We may as well carefully guide the postmarket  
15 surveillance of this product and how well it works.  
16 Clearly, we need carefully prescribed and intensive  
17 postmarketing required trials.

18 DR. BADEN: Dr. Baden. I voted no. The  
19 question was do we have substantial evidence of  
20 safety and efficacy? There are no efficacy data  
21 presented, and the historical efficacy data are too  
22 strong to allow a placebo trial, but too weak to

1 allow a noninferiority margin. So one is choosing  
2 which pieces of data to use to say that we cannot  
3 study this population.

4 I share the open public hearing speakers, as  
5 well as Dr. Siberry's comments we have failed  
6 women. To be at this point and not have the data  
7 to guide decision making is a shame on all of us.  
8 I feel like Arrowsmith. "We are in a desperate  
9 situation, therefore let's do something because we  
10 can do something."

11 There are side effects to our interventions.  
12 Our interventions are not benefit with no risk, and  
13 the presumption that we can benefit and not have  
14 risk is also shame on us. We need to generate some  
15 data to guide the risk-benefit ratio, and the road  
16 traveled for prevention in women is uneven with  
17 high-quality large studies done. So for us to  
18 presume that the good data are the ones we should  
19 hang our hat on is presumptuous.

20 I think that given the mixed historical  
21 data, the absence of data with this particular  
22 agent, I cannot support an indication which has

1 efficacy. On the other hand, there should be a  
2 mandated study. Whether it's mandated as part of  
3 an approval or mandated in order to get approval,  
4 both can be done, but it should be mandated.

5 I think once there's an approval, it's  
6 impossible to undo even if there's no benefit  
7 shown. If there's no approval, then the pressure  
8 is to do the study, but then there are women at  
9 risk who don't have opportunity to access this  
10 medication. Hence, we have failed this population.  
11 But I voted no because there were no data in the  
12 population in question.

13 Dr. Ofotokun?

14 DR. OFOTOKUN: Igho Ofotokun. I voted yes.  
15 Taking a look at the data as a whole, the Descovy  
16 data and the historical data from Truvada, based on  
17 data in HIV-infected individuals who are treated  
18 with Descovy, I am convinced that the product is  
19 just as safe in men and in women, and the big  
20 question is that of the efficacy in ciswomen.

21 I tend to have some confidence in the  
22 pharmacokinetic data and the correlate of Truvada

1 efficacy. The tenofovir diphosphate correlates  
2 with protection, I seem to believe that that in  
3 itself provides strong compelling data that TAF  
4 would be just as efficacious in ciswomen.

5 I agree that it's a terrible failure that  
6 the agency as well as the sponsor would come to  
7 this committee with lack of data for women in this  
8 hearing. I strongly believe, like others have  
9 expressed, that there should be a mandated study to  
10 look at women, ciswomen, either as part of the  
11 approval process or before the approval of this  
12 agent.

13 I also believe that approving Descovy for  
14 PrEP in men who have sex with men alone would  
15 create a two-tier system. It will just accentuate  
16 this equity, the equity issue that already exist;  
17 that either you're going to approve it for  
18 indication for prep in men and women, or you're not  
19 going to move forward with it.

20 I think creating a two-tier prevention  
21 treatment will not be helpful, and we should remind  
22 ourselves there are more women living with HIV in

1 the world than there are men, and that the risk of  
2 new infection is significantly higher among women  
3 if we look at this globally.

4 So I will stop there, and thank you.

5 DR. BADEN: Thank you. Dr. Burgess?

6 DR. BURGESS: Tim Burgess. I voted yes, but  
7 as some others have said, I very nearly voted no  
8 and very nearly abstained. I share concerns about  
9 what we think we understand about the putative  
10 mechanism of protection depending on route of  
11 exposure.

12 My overarching concern was about the public  
13 health impact of an indication in one population  
14 and not in another population. Coupled with the  
15 fairly compelling articulation of levels in PBMCs  
16 as the primary, if not total component of the  
17 likely mechanism of protection, led me to vote yes.  
18 I, like others, articulate a strong recommendation  
19 for, compelled postmarketing surveillance, focusing  
20 on effectiveness in women.

21 DR. BADEN: Dr. Le?

22 DR. LE: My vote for approval in cisgender

1 woman was largely based on three factors: one,  
2 data pertaining to vaginal tissue and PBMC as  
3 presented earlier by Dr. Read; two, some safety  
4 data but from other studies; and three, making this  
5 drug combination available as an option for women,  
6 not just for men, despite the lack of efficacy  
7 data.

8           However, my vote for yes is contingent upon  
9 full commitment from the applicant to incorporate a  
10 robust package labeling, stating that efficacy and  
11 effectiveness have not been established in  
12 cisgender women with the use of this product, and  
13 that vaginal tissue penetration was low, and that  
14 the approval was based on extrapolation of existing  
15 data in other populations.

16           Also, the applicant should commit to conduct  
17 robust postmarketing studies to allow for us to  
18 better understand efficacy and more effectiveness,  
19 as well as incorporating safety monitoring for  
20 weight gain, renal function, and on fasting plasma  
21 lipid levels.

22           DR. BADEN: Thank you. Dr. Walker?

1 DR. WALKER: Dr. Roblena Walker. It was a  
2 strong no for me, no wavering on the fence. I'm  
3 almost highly appalled. There's about 8 women on  
4 the committee, and that the agency and the  
5 applicant would present insufficient data to  
6 support the prevention of Descovy amongst  
7 cisgendered women, or heterosexual women, or just  
8 women in general, I was highly appalled that more  
9 dedication and passion wasn't put into the study.

10 DR. BADEN: Dr. Dodd?

11 DR. DODD: So I voted no, and I was not on  
12 the fence on this, unlike the last one. My concern  
13 is about confusion or a lack of trust that might be  
14 generated by an approval that wouldn't be supported  
15 by strong science. We can't approve something just  
16 because there's a need.

17 I also want to commend the agency for their  
18 good discussion about surrogacy. I think this is  
19 often a confusion in reviews of studies. There are  
20 lots of reasons why a good correlate of protection  
21 may fail as a surrogate endpoint for the clinical  
22 benefit endpoint. In this case, the clinical

1 benefit endpoint is protection.

2 A correlate does not a surrogate make, and  
3 we've seen data to support PBMCs as a good marker  
4 of protection and women -- or we've not seen the  
5 data; excuse me. And I thought the agency did a  
6 good job of providing some reasonable arguments  
7 about why PBMCs may not be a good marker of a  
8 clinical benefit endpoint.

9 I think there probably should be both data  
10 related to the biological mechanism supporting  
11 additional surrogacy studies -- this looks like  
12 more studies on tissue concentrations -- and  
13 additionally, studies in ciswomen with an actual  
14 clinical benefit endpoint of protection.

15 I'm not convinced that there's not a study  
16 design out there that could be considered that  
17 would support this. I don't know that it would  
18 have to be something as large as a 20,000  
19 participant study, but I think it's time to put  
20 some creative heads together and think of some  
21 feasible designs.

22 DR. BADEN: Dr. Giordano?

1 DR. GIORDANO: Tom Giordano. I voted no.  
2 It pains me to say that. I really wanted to vote  
3 yes because I believe there is the potential for  
4 creating two systems, and one drug for the rich,  
5 one for the poor, one for men, and one for women, I  
6 think that's a horrible precedent.

7 Nonetheless, the FDA's approval, to me,  
8 means we know this drug is safe and effective. I'm  
9 convinced we know this drug is safe in women, no  
10 doubt about that, but is it effective? That  
11 remains a hypothesis. And given that there's  
12 different biology involved between men and women  
13 and the acquisition of HIV in men and women, I  
14 think you need efficacy data, and it just boils  
15 down to that for me.

16 I think that we're in this position is  
17 absolutely horrible, but that's the position we're  
18 in. So I don't envy the agency's ultimate  
19 decision, but, to me, there is no way you can say  
20 this drug has efficacy in cisgendered women. And  
21 who's to blame for that? That's not my decision.

22 DR. BADEN: Dr. Daskalakis?

1 DR. DASKALAKIS: Demetre Daskalakis. I  
2 voted yes. I think that there are a couple of  
3 reasons. First, we have limited success with  
4 topical agents that we know of to prevent HIV, and  
5 I think we've seen data that intracellular levels  
6 of drug seem to be protective, so that in  
7 combination with what I thought was a pretty  
8 convincing explanation for the role of a PBMC  
9 level, intracellular level, and prevention made me  
10 feel that I had enough evidence to recommend that  
11 you consider approval for this drug for cisgender  
12 women.

13 Now, I would put the caveat that labeling  
14 would be very critical if it does come out like  
15 this, so I think it would need to be an alternative  
16 agent for women in certain clinical scenarios. And  
17 I also think that it would be important to state  
18 that there has not been an efficacy study done.  
19 Now, from the safety perspective, I agree with what  
20 everyone else has said, that I think safety has  
21 been demonstrated by other studies, and that's not  
22 really much of a debate.

1           I also want to say that I don't think the  
2 approval of this drug would increase PrEP uptake  
3 among women. So bottom line is that's not the  
4 problem, at least in the U.S. The size of the pill  
5 and the marginal improvement in bone and kidney  
6 outcomes, not the problem.

7           The problem is that patients and providers  
8 are unable to do appropriate assessment of who  
9 needs PrEP, and I'm just concerned that creating  
10 the tiered system that we may be creating if we  
11 don't approve the drug for women will create even  
12 more confusion with providers and poor advice to  
13 their female patients who are considering PrEP, so  
14 that makes me very concerned.

15           I think a mandatory study, no matter what,  
16 whether it is after approval or preapproval,  
17 requiring that is critical, and that needs to help  
18 answer this question about intracellular level  
19 versus mucosal level. So really good science that  
20 looks at the role of mucosal levels of tenofovir in  
21 women will be critical.

22           I also recommend thinking about coupling the

1 transgender female study with a women's study since  
2 they are women, and that probably is a better way  
3 to actually convince folks to enter the study. I  
4 bet you one reason you can't recruit a transgender  
5 study is because it says MSM, and that's not going  
6 to work.

7 Another thing I just want to bring up  
8 briefly is the precedent for extrapolating data.  
9 We have U.S. preventative health services  
10 recommendations that PrEP is an A recommendation,  
11 and there is a line in there that says that  
12 tenofovir could potentially be used as monotherapy  
13 to prevent PrEP in women and heterosexual males and  
14 females, and injection drug users.

15 I do not see us having a conversation about  
16 using a generic, cheaper agent and extrapolating  
17 that data to men who have sex with men, so we could  
18 actually pour PrEP onto the entire country and be  
19 less concerned about cost. So as we're having this  
20 conversation about an expensive new drug, I would  
21 encourage the agency to consider looking back at  
22 the Bangkok PrEP study, at TDF2, at Partners PrEP,

1 and ask the question, should we be asking the same  
2 thing about a drug that could cost as less as \$5 a  
3 month? Thank you.

4 DR. BADEN: Thank you. Dr. Read?

5 DR. READ: Sarah Read. I voted yes, but  
6 with a lot of the same hesitations that have been  
7 expressed by the other members who voted yes. Just  
8 to be clear, I also agree that it's extremely  
9 disappointing to be in a situation in which there  
10 are no clinical efficacy data in cisgender women, a  
11 population clearly in need of more effective  
12 prevention choices and in whom much remains to be  
13 learned regarding acceptability and preferences for  
14 prevention choices. However, I felt in this case  
15 that it was reasonable to extrapolate data from the  
16 DISCOVER trials as well as previous prevention  
17 trials with Truvada.

18 In terms of safety, although cisgender women  
19 were not included in the DISCOVER trial, I think  
20 it's reasonable to extrapolate safety from the  
21 study participants, as well as the large experience  
22 in treatment of women with HIV. And based on

1 treatment experience, I think that it's unlikely  
2 that the safety profile will differ in cisgender  
3 women relative to men.

4 In the absence of clinical efficacy data in  
5 cisgender women and the question of the relevance  
6 of PK in different compartments being not entirely  
7 clear, extrapolation of the efficacy of cisgender  
8 women is certainly not straightforward.

9 Although the collective data regarding PK  
10 levels and correlation of clinical efficacy of oral  
11 PrEP contain mixed results, I think it's reasonable  
12 to extrapolate the clinical efficacy seen with  
13 Truvada and Partners PrEP in cisgender women on the  
14 basis of the data provided by the applicant,  
15 indicating higher levels of TDF diphosphate in  
16 PBMCs with F/TAF compared to Truvada.

17 PK data provided by the applicant on  
18 cervical vaginal tissue levels, however, is less  
19 clear given the number of samples that are  
20 unevaluable. However, it's also unclear what  
21 levels are required in this tissue. I therefore  
22 think these data should largely be disregarded.

1           I think it would be problematic to approve  
2           an indication in men who have sex with men alone  
3           without including women. Such a limited indication  
4           and subsequent delay in access for women for many  
5           years would be untenable and an unfair situation.  
6           Consideration, therefore, I think should be given  
7           either to the approval with a broader indication to  
8           include women or no approval at all until evidence  
9           of adequate efficacy can be achieved in that  
10          population.

11           If an indication to include cisgender women  
12          is approved, like others, I recommend strongly that  
13          the applicant be required to perform trials to  
14          collect both safety and effectiveness data in this  
15          population. Not only is the effectiveness  
16          important, but also the safety profile in this  
17          population needs to be further supported.

18           I think it's important that the company has  
19          attested and pledged that they will perform these  
20          trials, and I think it's up to the agency to  
21          require them to do so.

22           DR. BADEN: Thank you. Dr. Smith?

1 DR. SMITH: I feel like we're moving  
2 backwards from the 2012 meeting that approved  
3 Truvada, in which there was a lot of discussion and  
4 concern that we had data on African women and not  
5 on African American women. And now we don't have  
6 data on women at all. The decision has been made  
7 that we'll do the trial in MSM, and then we'll  
8 figure out what it means for women rather than  
9 studying women themselves.

10 I find that bad science, and that's why I  
11 voted no, but I also find it disrespectful and an  
12 issue of sort of research equity. Women deserve  
13 the same quality of data about the safety and  
14 efficacy of the drugs that they're exposed to that  
15 men get, and that's not the situation we find  
16 ourselves in at the moment.

17 I also think that because we have Truvada  
18 approved for women, we're not denying women access  
19 to PrEP, and it's important to remember that. What  
20 we are doing is saying that a second drug that is  
21 similar in risk and benefit is available to one  
22 population but not another, yet, based on the data

1 that we have. I think that's preferable to  
2 approving it, doing an efficacy study and somebody  
3 suggested maybe taking it back or modifying it if  
4 it doesn't work out as well.

5 That's a recipe for disaster among the  
6 African American community if we get ourselves into  
7 a situation where we're approving something and  
8 then saying, oh well, no, actually we weren't  
9 right; that didn't work, so I wouldn't even think  
10 about doing that.

11 I think the other thing is that even though  
12 we think about the fact that it may be hard to  
13 explain why this is for this group and not for that  
14 group, if the proper studies are done in the short  
15 term over the next three or four years to get the  
16 kinds of data that is missing, then we'll be in a  
17 position to say whatever is appropriate about  
18 women.

19 I think we are going to increasingly in the  
20 PrEP field have this situation of some things are  
21 for some people and other things are for other  
22 people. Whether that's the dapivirine ring, if

1 that becomes approved, that's surely not going to  
2 be for all populations. I know we're nervous about  
3 what that means when we suddenly have to start  
4 making decisions, but I think this is not the  
5 occasion in which that should overrule the absence  
6 of data on efficacy for women as the basis for our  
7 decision.

8 DR. BADEN: Dr. Goetz?

9 DR. GOETZ: Matthew Goetz. I did vote yes,  
10 and I think I'm like the other 8 people who voted  
11 yes. I do not hear a strong ringing endorsement  
12 from anyone of strong data. I read the statement,  
13 "allow for expansion" as a liberal statement,  
14 "allow for expansion."

15 I thought critically about what we know  
16 about surrogate markers, correlates of protection.  
17 I think "correlate" is the right word in many  
18 regards. The fact of the matter is that we will  
19 need a phase 4 mandated clinical trial to  
20 substantiate that this is I think an alternative,  
21 and in any guidelines, documents, that are produced  
22 by other societies, the strengths and weaknesses of

1 this, the conditional nature, and this is an  
2 alternative needs to be very clear.

3 I felt very strongly that I'm not sure that  
4 tissue markers are the surrogate either. As has  
5 been pointed out by many individuals, when we  
6 biopsy, first of all, we get very limited samples.  
7 It's not robust. Secondly, the cells that we  
8 sample are not likely the relevant cells. So we  
9 either need robust data showing across levels of  
10 different adherence, and we want everyone to be  
11 adherent of course.

12 Inevitably, some people are going to be less  
13 adherent, and we need to be able to correlate if  
14 we're going to substantiate in any way. PBMCs show  
15 that the correlate between PBMC and protection is  
16 similar across all the relevant risk groups, and I  
17 think that will go a long ways to demonstrating  
18 what we need to show here.

19 Perhaps finally -- I can go on for a lot  
20 long longer -- I think adherence is a crucial  
21 measure. What we have in this drug and the study  
22 we have in DISCOVER is a population that was

1       extraordinarily adherent. That's wonderful, but we  
2       need to be clear that we want to really emphasize  
3       adherence throughout. TAF may have a longer  
4       half-life than plasma in cells, but that is not to  
5       be taken as any opportunity to be less adherent;  
6       phase 4 studies absolutely mandated.

7               DR. BADEN: Thank you. There you have it, 8  
8       to 10 vote. The three key principles as I hear it,  
9       because I will summarize the yes and the nos  
10       together, the correlate is unclear and perceived  
11       differently. The optics of approving for  
12       population A but not population B has many  
13       deleterious effects if done or not done. Everyone  
14       agrees there needs to be actual data.

15               So then the challenge -- and I'll be  
16       presumptuous, but I'll speak for the committee, and  
17       to the agency, and to the applicant -- can you  
18       please do the study as quickly as possible? And  
19       it'd be designed -- I don't accept that it's too  
20       hard, too big, too difficult.

21               There should be a way to do some type of  
22       study systematically in a reasonable amount of time

1 if there's collective will to generate data  
2 expeditiously, and that will be the best way to  
3 minimize the optics of some of the concerns raised.  
4 Many of us believe that this should work and will  
5 work, but we cannot have belief guide policy or  
6 regulatory pathway.

7 So that is the voting segment. We have run  
8 15 minutes over. I would like to take 5 minutes to  
9 discuss the last question, and that will be an open  
10 discussion unless the agency advises me otherwise.  
11 The open discussion is please discuss whether the  
12 data from the DISCOVER trial are relevant to  
13 at-risk men who practice insertive vaginal sex with  
14 cisgender women.

15 I'll open the discussion and look for  
16 disagreement or augmentation. There are many  
17 aspects of insertive vaginal sex that have elements  
18 that are analogous to MSM in the sense of the  
19 biology of how the drug works and the nature of the  
20 exposure. We weren't able to extract out MSM with  
21 only insertive, but presumably there will be some  
22 of that in the population -- it was a large

1 population -- and the biology in the prior  
2 experience is such that I don't think it's  
3 unreasonable to think that it's likely to work in  
4 that population.

5 But I would like other comments from the  
6 committee as to if others agree that it should  
7 likely work in that population or if there are  
8 concerns as to why it may not.

9 DR. SWAMINATHAN: Just to make clear, we're  
10 talking about HIV, uninfected men having sex with a  
11 discordant partner, female partner.

12 DR. BADEN: Yes, and circumcision has not  
13 been addressed, but presumably the other preventive  
14 strategies will be maximally encouraged.

15 Dr. Siberry?

16 DR. SIBERRY: I agree with your general view  
17 that this can be extrapolated, but I do think that  
18 the data should be looked at more carefully from  
19 the DISCOVER trial. They enrolled people who had  
20 condomless anal sex, not just condomless receptive  
21 anal sex. So I think if they had collected  
22 information about practices, you may be able to

1 segregate those practices, predominantly insertive  
2 sex from those who didn't, look at it stratified by  
3 condoms, and see if there was a difference in the  
4 protective -- the levels of infection in the two  
5 arms.

6           Granted, the overall infection risks are  
7 probably lower in both arms of that group if you  
8 limit it to those, but I think we should ask for  
9 additional scrutiny of data.

10           DR. BADEN: And perhaps new data to actually  
11 look at that population.

12           DR. SIBERRY: Yes.

13           DR. BADEN: Dr. Gripshover?

14           DR. GRIPSHOVER: I'm sorry. I didn't  
15 realize there's still a vote, but I do think the  
16 fact that 44 percent were uncircumcised means that  
17 at least there was a group that had not yet even  
18 used that other protective mechanism, so that's I  
19 think helpful, too.

20           DR. BADEN: Dr. Weina?

21           DR. WEINA: Given the way the trial was  
22 enrolled, the data's just not there. So I'm not

1       sure that you can actually extrapolate anything  
2       from that trial.

3               DR. BADEN:  So what is your view, then, on  
4       the applicability to men who have vaginal sex?

5               DR. WEINA:  I think it's just like -- well,  
6       in my patient population, I have individuals that I  
7       have in my patient population that are at high  
8       risk, and in heterosexual relationships, and come  
9       to me and are actually on Truvada for preventive  
10       reasons, but the data is not really there to  
11       support it.  It just makes sense based upon the  
12       data that is out there.

13               So there's an extrapolation because the  
14       individual is at very high risk, and everything  
15       that we can do to help prevent it is going to be  
16       something that's worthwhile as long as they're  
17       properly informed as to the risks associated with  
18       taking the medication as well.

19               DR. BADEN:  Well, let me push you a little  
20       bit on that --

21               DR. WEINA:  Sure.

22               DR. BADEN:  -- in that if you have MSM who

1 have insertive and receptive, presumably the  
2 insertive risk would be similar to the insertive  
3 risk in non-anally receptive.

4 DR. WEINA: Agree.

5 DR. BADEN: So therefore, if data suggest  
6 that it works in that population, even those not  
7 specifically pulled out, that would be suggestive  
8 that it is likely to work in that population.

9 DR. WEINA: so again, just like I was  
10 talking about before, suggestive and correlates and  
11 surrogate markers and everything else are --

12 DR. BADEN: Although, I think it's a little  
13 different. These are human data --

14 DR. WEINA: True.

15 DR. BADEN: -- in men who are in study on  
16 drug and not getting infected.

17 DR. WEINA: True.

18 DR. BADEN: This is not extrapolating from  
19 assays that we're not completely sure what they  
20 tell us with a correlate, that we're not sure what  
21 it tells us in 5 people.

22 DR. WEINA: True. So given the potential

1 outcome of not putting the individual on Truvada,  
2 when they come to me with exceedingly high risky  
3 behavior with multiple unknown partners on a  
4 regular basis, I inform them of the risks  
5 associated with it and the potential benefits --

6 DR. BADEN: And the limitations of the data.

7 DR. WEINA: -- and allow them to make the  
8 decision.

9 Dr. Daskalakis?

10 DR. DASKALAKIS: Just fusing this issue a  
11 bit with the issue about the need for a study in  
12 women, it seems as if there's a need for another  
13 serodiscordant heterosexual study like a Partners  
14 PrEP but that uses this drug.

15 DR. BADEN: Although part of a challenge  
16 there is treatment as prevention.

17 DR. DASKALAKIS: Right, but still --

18 DR. BADEN: But still --

19 DR. DASKALAKIS: There's an environment  
20 where it's still feasible with lower edge  
21 retroviral uptake, so it wouldn't necessarily  
22 launch that study --

1 DR. BADEN: But generating the data makes  
2 sense.

3 DR. DASKALAKIS: But I think that there's  
4 other parts of the world where you can have  
5 serodiscordant couples and follow that, realizing  
6 that there will be -- that the sample size will  
7 probably have to be bigger and the effect may be  
8 smaller.

9 DR. WEINA: But the point is that there are  
10 parts of the world in which this could be done just  
11 like we do malaria studies in other parts of the  
12 world because we haven't got a whole lot of malaria  
13 here in the United States to get new drugs  
14 approved.

15 DR. BADEN: Dr. Swaminathan?

16 DR. SWAMINATHAN: I guess the difference to  
17 me is that there's a little bit more that you can  
18 extrapolate from. You have data in discordant  
19 couples where the woman is positive that tenofovir  
20 works, and MSM couples it works, and we have  
21 evidence that TAF works in MSM couples.

22 So now you're just sort of bringing in the

1 fourth variable or a mix of those two variables to  
2 say, well, TDF works for this situation and TAF  
3 works for this situation, and TDF also works for  
4 this situation, which is -- you can sort of  
5 extrapolate a little bit more from that, that you  
6 would expect the person who was protected by TDF in  
7 the Partners study to be protected by TAF in the  
8 future.

9 DR. BADEN: Dr. Goetz?

10 DR. GOETZ: I think another piece of  
11 supporting evidence is the incidence of gonococcal  
12 urethritis and other urethritis in the patient  
13 population, which I think was 15 to 20 percent  
14 thereabouts. So there was substantive exposure  
15 to -- evidence of insertive practices.

16 Yet, if I recollect the data properly, all  
17 the cases of infection were amongst those people  
18 who clearly had receptive anal intercourse. The  
19 presence of the urethritis I think is a strong  
20 piece of evidence in favor of the fact that there  
21 was risk in the patient population.

22 DR. BADEN: Dr. Smith?

1 (Dr. Smith gestures no.)

2 DR. BADEN: So I think that that touches on  
3 a lot of the key issues around this question. Are  
4 there any other issues the agency would like us to  
5 address?

6 (No response.)

7 DR. BADEN: If not, then I would like to  
8 thank the applicant for a tremendous amount of data  
9 being presented and entertaining a lot of  
10 discussion in a challenging area; the agency for  
11 sharing your views in the challenge here; the panel  
12 members for a robust, high energy day in covering a  
13 lot of complex issues; and the public as well for  
14 sharing your thoughts.

15 I'll see if the agency has any closing  
16 remarks.

17 DR. BIRNKRANT: Well, I, too, on behalf of  
18 our division and the agency, want to thank the  
19 committee for their thoughtful discussion and  
20 deliberations today. I also want to thank the  
21 speakers who commented during the open public  
22 hearing as well. I want to thank the company for

1 conducting the DISCOVER study and other pertinent  
2 research and for committing earlier in the day to  
3 conduct a trial, or trials, in women.

4 I also want to thank the trial participants  
5 as well. Lastly, I'd like to thank our staff for  
6 their dedication and diligence in conducting the  
7 reviews and preparing for this committee. I want  
8 to leave you with a couple thoughts before we end.  
9 Our review of this application continues. We have  
10 not made any final determinations as of today, and  
11 your comments and the discussions will greatly  
12 impact our final determination.

13 Lastly, I feel like we should dedicate our  
14 collective efforts to ensuring the availability of  
15 safe and effective medications for all populations  
16 so that the next time we meet, we can definitively  
17 state that the HIV incidence in the United States  
18 has substantially declined in all populations, and  
19 we are moving closer to defeating this epidemic.  
20 Thank you very much.

21 **Adjournment**

22 DR. BADEN: Thank you, and I will now

1 adjourn the meeting. Safe travels.

2 (Whereupon, at 4:54 p.m., the meeting was  
3 adjourned.)

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