Descovy® for PrEP

Antimicrobial Drugs Advisory Committee Meeting
August 7, 2019
NDA 208215/S-012
Introduction

Diana Brainard, MD
Senior Vice President
HIV & Emerging Viruses
# Truvada® and Descovy®

<table>
<thead>
<tr>
<th>Components</th>
<th>Truvada</th>
<th>Descovy</th>
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<tbody>
<tr>
<td>Emtricitabine (FTC)</td>
<td></td>
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<tr>
<td>Tenofovir disoproxil fumarate (TDF)</td>
<td></td>
<td>Tenofovir alafenamide (TAF)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications</th>
<th>Truvada</th>
<th>Descovy</th>
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<tbody>
<tr>
<td>HIV treatment (as part of a complete regimen) in adults and adolescents</td>
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<tr>
<td>HBV treatment (TDF alone)</td>
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<td>HBV treatment (TAF alone)</td>
</tr>
<tr>
<td>PrEP in adults and adolescents</td>
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<td>PrEP in adults and adolescents</td>
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</tbody>
</table>

HBV=hepatitis B virus.
Tenofovir Alafenamide: Longer Half-Life Allows for Lower Dose

Plasma TFV levels 90% lower with TAF vs TDF

GI=giastrointestinal; PBMC=peripheral blood mononuclear cell; TFV=tenofovir.


Tenofovir Alafenamide: Higher Diphosphate Levels in PBMCs

TFV-DP=tenofovir diphosphate.

Mechanism of Action for Tenofovir Disphosphate (TFV-DP)
Active Metabolite of TDF and TAF

A=adenosine; C=cytosine; DNA=deoxyribonucleic acid; G=guanine; RT=reverse transcriptase; U=uridine.
Mechanism of Action for Tenofovir Disphosphate (TFV-DP)
Active Metabolite of TDF and TAF

A=adenosine; C=cytosine; G=guanine; RT=reverse transcriptase; U=uridine.
Descovy and Truvada TFV-DP Levels in PBMCs
Phase 1 Study in Healthy Volunteers

EC$_{90}$=90% effective concentration (40 fmol/10$^6$ cells, Anderson PL, et al. CROI 2012); IQR=interquartile range.
a. DVY data from bictegravir/F/TAF 50/200/25 mg in volunteers (N=26) and TVD data from Schwartz JL, et al. HIV Research for Prevention 2018 (n=25), Cottrell 2017; b. Mean simulated time to steady state.
TFV-DP Levels Over Time Once Dosing Stops
Simulation of Descovy vs Truvada Based on Observed TFV-DP at Steady State

TFV-DP Levels in Rectal Tissue

BLQ=below limit of quantification.
4 different rectal samples were collected for each participant at 4h postdose. 8/28 DVY samples BLQ; 1/28 TVD samples BLQ. Schwartz JL, et al. HIV Research for Prevention 2018, updated unpublished data.
Mechanism of Sexually Acquired HIV Infection
Virus Breaches the Epithelium

Mechanism of Sexually Acquired HIV Infection

Infiltration of T Cells

Initial Infection

Infiltration of T cells

Mechanism of Sexually Acquired HIV Infection

Focus of Infection

Mechanism of Sexually Acquired HIV Infection
Dissemination to Lymph Nodes

- Initial Infection
- Infiltration of T cells
- Founder population
- Dissemination of infection via lymphatic system

- Dendritic/Langerhans cell
- Plasmacytoid dendritic cell
- HIV virus
- CD4+ T cell
- Infected CD4+ T cell
- PBMC
- Chemokines

Mechanism of Topical vs Systemic Prevention Intervention

1. Drug absorbed into local tissues/cells
2. Efficacy among high adherers 54%1

Systemic Agents

1. Drug diffuses into local tissues/cells; PBMCs with drug reach tissues
2. Efficacy among high adherers 99%2

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PBMC TFV-DP Levels and HIV Risk Reduction

CI=confidence interval; PY=person-year.
Truvada vs Descovy for PrEP in 2015

**Context**

1. Truvada for PrEP was approved in adults only
2. Descovy was undergoing FDA review for approval for HIV treatment
3. Data suggested low rectal tissue levels; ongoing debate regarding which compartment correlated with protection

**Purpose**

Conduct a statistically rigorous Phase 3 study to definitively establish the safety and efficacy of Descovy for PrEP in MSM and transwomen
Phase 3 DISCOVER Trial Design

- International, double-blind, randomized, active-controlled, noninferiority study comparing Descovy with Truvada for PrEP
- Enrolled 5387 cismen and transgender women who have sex with men and are at high risk of HIV
- Designed in close collaboration with FDA and the community
DISCOVER Trial: Key Findings

- Primary endpoint met: Descovy was noninferior to Truvada
  - 7 infections (0.16 per 100 PY) with Descovy
  - 15 infections (0.34 per 100 PY) with Truvada

- The incidence rate ratio was 0.47 and the upper bound of the confidence interval was 1.15, less than the prespecified noninferiority margin of 1.62

- Descovy was superior to Truvada on 6 prespecified, alpha controlled secondary safety endpoints, including markers of bone and renal toxicity
Truvada vs Descovy for PrEP in 2019

Context

1. For both Truvada and Descovy, adherence is the key determinant of efficacy.
2. Correlate of protection established for PBMC TFV-DP levels.
3. Truvada rectal tissue levels 10-fold higher than Descovy; Descovy PBMC TFV-DP levels 7-fold higher than Truvada.
4. DISCOVER point estimate suggests possible efficacy advantage for Descovy.

Implication

PBMC drug levels drive efficacy for Truvada and Descovy.
Efficacy of Truvada for PrEP in Women

- Clinical trials of Truvada for PrEP have shown heterogeneous efficacy related to highly variable rates of adherence.
- Controlling for adherence, Truvada is equally and highly effective in men and women.
- Biology of HIV transmission is independent of gender:
  - Virus only replicates in mononuclear cells.
  - Systemic transmission requires recruitment of target cells from the periphery to the site of initial infection.
- Adequate drug levels within mononuclear cells are necessary and sufficient to mediate protection against HIV infection.

DISCOVER Results Are Relevant for Ciswomen

- Efficacy and safety for HIV treatment well established in >2,000 women and similar to men in clinical trials
- HIV behaves similarly in men and women
- Descovy and Truvada inhibit HIV in CD4+ T cells through the same active metabolites in men and women
- Pharmacokinetics similar irrespective of HIV status, sex
- Data support Descovy for PrEP in ciswomen
DISCOVER Results Are Relevant for Adolescents

- Descovy and 3 Descovy-based single tablet regimens approved in adolescents for HIV treatment based on established safety and efficacy in this group
- HIV behaves similarly in adolescents and adults
- Similar Descovy pharmacokinetics and pharmacodynamics in DISCOVER participants and adolescents with HIV
- Data support Descovy for PrEP in adolescents
Proposed Indication

Descovy is indicated:

- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg
- for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg
# Agenda

## Introduction
- **Diana Brainard, MD**
  - Senior Vice President
  - HIV and Emerging Viruses
  - Gilead Sciences, Inc.

## DISCOVER Study Design, Treatment Population, and Efficacy Results
- **Scott McCallister, MD**
  - Executive Director
  - HIV and Emerging Viruses
  - Gilead Sciences, Inc.

## DISCOVER Safety and Descovy for PrEP for Women and Adolescents
- **Moupali Das, MD, MPH**
  - Executive Director
  - HIV and Emerging Viruses
  - Gilead Sciences, Inc.

## Clinical Context
- **Richard Elion, MD**
  - Director of Research
  - Washington Health Institute
  - Clinical Professor of Medicine
  - George Washington University
# DISCOVER Response Team

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
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<tbody>
<tr>
<td>Clinical Pharmacology</td>
<td>Anita Mathias, PhD</td>
</tr>
<tr>
<td>Nonclinical Safety</td>
<td>Anne Chester, PhD</td>
</tr>
<tr>
<td>Risk Management</td>
<td>Terry Farrow, MD</td>
</tr>
<tr>
<td>Statistics</td>
<td>Michael Wulfsohn, MD, ScD</td>
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<tr>
<td>Virology</td>
<td>Christian Callebaut, PhD</td>
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<tr>
<td>External Pharmacoadherence Specialist</td>
<td>Peter Anderson, PharmD</td>
</tr>
<tr>
<td></td>
<td>Professor, Department of Pharmaceutical Sciences</td>
</tr>
<tr>
<td></td>
<td>Skaggs School of Pharmacy and Pharmaceutical Sciences</td>
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<td>University of Colorado Anschutz Medical Campus</td>
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Study Design, Treatment Population, and Efficacy Results

Scott McCallister, MD
Executive Director, Clinical Research
HIV & Emerging Viruses
Study Design

Primary analysis is HIV incidence per 100 person years when
- 100% complete Week 48
- 50% complete Week 96

- Blinded until all participants reach Wk 96
- Open-label switch to DVY offered after Wk 96

Descovy QDa
n=2694

Truvada QDb
n=2693

MSM or TGW Adults ≥18 y
Randomized Double-blinded Active controlled

1:1

QD=once daily; TGW=transgender women.
a. F/TAF dose: 200/25 mg; pill size 12 x 6 mm; b. F/TDF dose: 200/300 mg; pill size 19 x 8 mm.
Eligibility Criteria

- High sexual risk of HIV
  - \( \geq 2 \) episodes of condomless anal sex (>1 unique partner), in the 12 weeks prior to enrollment
  - OR
  - Diagnosis of rectal gonorrhea, rectal chlamydia, or syphilis, in the 24 weeks prior to enrollment

- HIV negative (prior PrEP use allowed), HBV negative

- Creatinine clearance \( \geq 60 \text{ mL/min} \)
Site Selection

Criteria

- High community incidence of HIV
- Cultural competency with populations at risk for HIV, ability to enroll and retain persons of color and transgender women

Conducted in cities with high HIV incidence

- 94 sites in 11 countries
- Participants:
  - 60% in US
  - 34% in EU
  - 7% in Canada
Study Protocol Development

- Study design discussed with: lead investigators, DISCOVER investigators, community, and FDA.

GCP=good clinical practice; GLP=good laboratory practice; GMP=good manufacturing practice.
Primary Efficacy Endpoint

- HIV incidence rate (events per 100 PY) = $\frac{\text{Number of HIV Infections}}{\text{Person Years Exposure}} \times 100$
Primary Efficacy Endpoint

- HIV incidence rate (events per 100 PY) = \( \frac{\text{Number of HIV Infections}}{\text{Person Years Exposure}} \times (100) \)

- \( \frac{\text{HIV incidence rate, DVY arm}}{\text{HIV incidence rate, TVD arm}} \) = Incidence Rate Ratio (IRR)
Primary Efficacy Endpoint

- HIV incidence rate (events per 100 PY) = \( \frac{\text{Number of HIV Infections}}{\text{Person Years Exposure}} \times (100) \)

- \( \frac{\text{HIV incidence rate, DVY arm}}{\text{HIV incidence rate, TVD arm}} = \text{Incidence Rate Ratio (IRR)} \)

- Noninferiority margin = 1.62, preserves 50% of TVD effect in 3 prior RCTs in MSM

- DVY noninferiority to TVD established if the upper bound of the IRR 95% CI is less than 1.62

RCT=randomized controlled trial.
On Study Safety Testing

Safety assessments

- General safety evaluation (each visit)
- Renal labs, urine proteins (each visit)
- BMD tests of hip & spine (every 48 weeks)
- STI testing (each visit)

BMD=bone mineral density; STI=sexually transmitted infection.
### Safety assessments

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>General safety evaluation</td>
<td>(each visit)</td>
</tr>
<tr>
<td>Renal labs, urine proteins</td>
<td>(each visit)</td>
</tr>
<tr>
<td>BMD tests of hip &amp; spine</td>
<td>(every 48 weeks)</td>
</tr>
<tr>
<td>STI testing</td>
<td>(each visit)</td>
</tr>
</tbody>
</table>

### Prespecified Secondary Safety Endpoints (α-controlled)

1. Hip BMD % change from baseline
2. Spine BMD % change from baseline
3. Urine β2M:Cr % change from baseline
4. Urine RBP:Cr % change from baseline
5. Distribution of UPCR categories
6. Serum Cr (eGFR<sub>CG</sub>) change from baseline

β2M:Cr=β2-microglobulin:creatinine ratio; Cr=creatinine; eGFR<sub>CG</sub>=estimated glomerular filtration rate by Cockcroft-Gault method; RBP:Cr=retinol-binding protein:creatinine ratio; UPCR=urine protein:creatinine ratio.
On Study Evaluation of Sexual Behavior and Adherence

- Confidential questionnaires completed at screening and at each on study visit
  - Type and frequency of sexual events, condom use and drug adherence
- Site staff unaware of responses

- Support from site staff at each on study visit
  - Prevention education, risk reduction counseling
  - Condoms, lubricant provided
- Drug adherence support at each on study visit
  - Could also receive daily text reminders, and opt in/opt out at any time
On Study Adherence Evaluations

Subjective Testing

- All study participants: confidential questionnaire, and pill counts from returned bottles at all on-study visits

Objective Testing

- Dried blood spot substudy: randomly selected subset (n=540), collected at all on study visits
  - TFV-DP levels in RBCs
  - These levels provide information on adherence in the past 8 weeks before collection¹

RBC=red blood cell.

On Study Case-Control Analysis

HIV diagnosis ➔ 5 matched controls

Matched on geography, timing of HIV diagnosis, and diagnosis of a rectal STI
On Study Case-Control Analysis

Matched on geography, timing of HIV diagnosis, and diagnosis of a rectal STI

HIV diagnosis

5 matched controls

Dried Blood Spot Testing of TFV-DP (adherence)

Visits Every 12 Weeks

HIV Diagnosis
Participant Disposition: Screening to Data Analysis

All Individuals Screened, Randomized, Treated

- Met eligibility criteria, but not randomized\(^a\) n=94
- Screened, N=5857
- Randomized, n=5399
- Did not meet eligibility criteria, were not randomized, n=364
- Tested HIV positive at screening, n=49

DVY randomized n=2700
- DVY randomized, not treated\(^b\) n=6
- Still on study n=2295

TVD randomized n=2699
- TVD randomized, not treated\(^b\) n=6
- Still on study n=2328

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a. Reasons (n) were: lost to follow-up (32); withdrew consent (51); investigator’s discretion (3); outside of visit window (6); enrollment closed (1); participant death (1).
b. Reasons (n) were: protocol violation (1); withdrew consent (8); HIV-1 infection (2); investigator’s discretion (1).
## Baseline Demographics

<table>
<thead>
<tr>
<th>Age</th>
<th>Median, y (range)</th>
<th>DVY n=2694</th>
<th>TVD n=2693</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>34 (18–76)</td>
<td>34 (18–72)</td>
</tr>
<tr>
<td>&lt;25 y, n (%)</td>
<td></td>
<td>336 (12)</td>
<td>293 (11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race, n (%)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>White</td>
<td></td>
<td>2264 (84)</td>
<td>2247 (84)</td>
</tr>
<tr>
<td>Blacka</td>
<td></td>
<td>240 (9)</td>
<td>234 (9)</td>
</tr>
</tbody>
</table>

| Ethnicity, n (%) |                   |            |            |
|                  | Hispanic or Latinx| 635 (24)   | 683 (25)   |

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<tr>
<th>Gender, n (%)</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Transgender women</td>
<td></td>
<td>45 (2)</td>
<td>29 (1)</td>
</tr>
</tbody>
</table>

| Sexual orientation, n (%) |                   |            |            |
|                          | Gay                | 2461 (92)  | 2434 (91)  |
|                           | Bisexual           | 171 (6)    | 214 (8)    |
|                           | Heterosexual       | 25 (1)     | 16 (1)     |

a. includes mixed black race.
## Baseline Sexual Behavior

<table>
<thead>
<tr>
<th>Participants, %</th>
<th>DVY n=2694</th>
<th>TVD n=2693</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 receptive condomless anal sex partners, past 12 weeks</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>Rectal gonorrhea, past 24 weeks</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Rectal chlamydia, past 24 weeks</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Syphilis, past 24 weeks</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Recreational drug use, past 12 weeks</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Binge drinking&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Any prior use of TVD for PrEP</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Using TVD for PrEP at baseline</td>
<td>17</td>
<td>16</td>
</tr>
</tbody>
</table>

<sup>a</sup> ≥6 drinks on ≥1 occasion, at least monthly.
On Study Sexual Behavior

**Condomless Receptive Anal Sex Partners**
(Number Since Last Visit)

**Sexually Transmitted Infection Results**

- Consistently high sexual behavior rate in study participants led to high rates of STIs.
- 57% had gonorrhea or chlamydia diagnosed from any anatomic site (lab test) on study.
- STI rates of gonorrhea, chlamydia or syphilis (AE report) on study:
  - DVY arm, 145 per 100 PY
  - TVD arm, 139 per 100 PY

SD=standard deviation.
# Disposition at Time of Primary Endpoint Evaluation

<table>
<thead>
<tr>
<th>Participants, n (%)</th>
<th>DVY n=2694</th>
<th>TVD n=2693</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still on study drug</td>
<td>2242 (83)</td>
<td>2263 (84)</td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td>452 (17)</td>
<td>430 (16)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>201 (7)</td>
<td>170 (6)</td>
</tr>
<tr>
<td>Participant decision</td>
<td>193 (7)</td>
<td>175 (6)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>36 (1)</td>
<td>49 (2)</td>
</tr>
<tr>
<td>Nonadherence</td>
<td>8 (&lt;1)</td>
<td>12 (&lt;1)</td>
</tr>
<tr>
<td>Investigator discretion</td>
<td>5 (&lt;1)</td>
<td>10 (&lt;1)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>4 (&lt;1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Death(^a)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

*a. 1 of 3 deaths occurred after study drug discontinuation.*
Primary Efficacy Endpoint: Noninferiority Achieved

- 22 HIV infections diagnosed in 8756 PY of follow-up
- Rate ratio: 0.47 (95% CI: 0.19, 1.15)
Primary Efficacy Endpoint: Noninferiority Achieved

Incidence Rate Ratio (95% CI)

Favors DVY

Favors TVD

NI=noninferiority; RR=rate ratio.
Primary Efficacy Endpoint Details

22 HIV Infections

At or Before Study Entry

On Study Infections

- DVY: n=7
  - On study infections: 6 (1 suspected baseline infection)
  - Suspected baseline infection: 1

- TVD: n=15
  - On study infections: 4 (11 suspected baseline infections)
  - Suspected baseline infection: 4

On study infections

Suspected baseline infection
Primary Efficacy Endpoint Sensitivity Analysis
Excluding Baseline Infections

- Excluding 5 baseline infections (DVY=1, TVD=4):
  DVY incidence rate, 0.14 per 100 PY; TVD incidence rate, 0.25 per 100 PY
- Rate ratio=0.55 (95% CI: 0.20, 1.48)
## HIV Incidence Rate Ratios: Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Incidence Rate, Per 100 PY (95% CI)</th>
<th>Incidence Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>DVY: n=2670 0.16 (0.1, 0.3)</td>
<td>0.47 (0.19, 1.15)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=2665 0.34 (0.2, 0.6)</td>
<td></td>
</tr>
<tr>
<td>Age &lt;25 y</td>
<td>DVY: n=329 0.82 (0.2, 2.1)</td>
<td>1.23 (0.28, 5.49)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=289 0.66 (0.1, 1.9)</td>
<td></td>
</tr>
<tr>
<td>Age ≥25 y</td>
<td>DVY: n=2341 0.08 (0.0, 0.2)</td>
<td>0.25 (0.07, 0.90)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=2376 0.31 (0.2, 0.5)</td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td>DVY: n=234 0.27 (0.0, 1.5)</td>
<td>0.33 (0.03, 3.15)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=225 0.82 (0.2, 2.4)</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>DVY: n=1573 0.08 (0.0, 0.3)</td>
<td>0.17 (0.04, 0.77)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=1604 0.45 (0.2, 0.8)</td>
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</tr>
<tr>
<td>Ex-US</td>
<td>DVY: n=1097 0.28 (0.1, 0.7)</td>
<td>1.60 (0.38, 6.68)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=1061 0.18 (0.0, 0.5)</td>
<td></td>
</tr>
<tr>
<td>Recreational drug use</td>
<td>DVY: n=1771 0.21 (0.1, 0.5)</td>
<td>0.60 (0.22, 1.66)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=1768 0.35 (0.2, 0.6)</td>
<td></td>
</tr>
<tr>
<td>Binge alcohol use</td>
<td>DVY: n=1466 0.08 (0.0, 0.3)</td>
<td>0.29 (0.06, 1.41)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=1495 0.29 (0.1, 0.6)</td>
<td></td>
</tr>
<tr>
<td>≤3 URAI partners</td>
<td>DVY: n=1843 0.10 (0.0, 0.3)</td>
<td>0.39 (0.10, 1.47)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=1891 0.26 (0.1, 0.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 URAI partners</td>
<td>DVY: n=735 0.33 (0.1, 0.9)</td>
<td>0.52 (0.15, 1.78)</td>
</tr>
<tr>
<td></td>
<td>TVD: n=678 0.64 (0.3, 1.3)</td>
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URAI=unprotected receptive anal intercourse.
Primary Efficacy Endpoint Details, Resistance

22 HIV infections

19 samples genotyped

4 samples with resistance to study drugs detected

Resistance in DVY arm: 0

Resistance in TVD arm: 4
- All M184
- All with baseline infection
- All suppressed on effective ART

ART=antiretroviral therapy.
Adherence Results: Self Reports, Pill Counts
Full Analysis Set

**Self-report**

- Adherence %
- Median Adherence
- Participants, %

**Pill Count**

- Adherence %
- Median Adherence
- Participants, %

DISCOVER
Adherence by TFV-DP Levels in Dried Blood Spots
PK Cohort Analysis Set (n=536)

Descovy

Truvada

Tablets/wk
≥4
2–3
<2

Week
12
24
36
48
60
72
84
96

Participants, %

PK=pharmacokinetic.
Case Control: Adherence by TFV-DP Levels in Dried Blood Spots

- Median TFV-DP levels significantly lower in participants diagnosed with HIV (cases) than uninfected matched controls (p=0.001)
  - DVY: cases, 277 fmol/punches (IQR: 13, 474); controls, 1736 (1382, 2358)
  - TVD: cases, 133 fmol/punch (13, 755); controls, 1075 (735, 1612)

<table>
<thead>
<tr>
<th></th>
<th>DVY</th>
<th>TVD</th>
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<tbody>
<tr>
<td></td>
<td>Cases n=7</td>
<td>Controls n=34</td>
</tr>
<tr>
<td>Proportion with TFV-DP levels at &lt;2 doses/week</td>
<td>71%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Pharmacokinetic Data: Week 4 TFV-DP Levels in PBMCs

C_{tau}=trough concentration.

Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.


CC-55
Pharmacokinetic Data: Week 4 TFV-DP Levels in PBMCs

Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.

Efficacy Conclusions

- Descovy was noninferior to Truvada for HIV prevention
  - DISCOVER population at high risk of HIV infection
  - Low HIV incidence rates in both arms
- Low adherence was the most significant risk factor for HIV infection
- There was no resistance observed in the Descovy arm, 4 cases of M184 reported in the Truvada arm
- Significantly more participants in the Descovy arm reached the $EC_{90}$ in PBMCs than in Truvada arm
DISCOVER Safety

Moupali Das, MD, MPH
Executive Director
HIV and Emerging Viruses
Descovy: Safety Profile

- Safety and tolerability thoroughly established in HIV and HBV treatment
  - >26,000 PY in clinical trials
  - >1.6 million PY in clinical experience
- Improved renal and bone safety profile compared with Truvada
  - Favorable renal and bone biomarkers correlate with fewer clinical events
- DISCOVER confirms similar safety benefits in HIV-uninfected people
Descovy and Truvada Exposure

- At the primary endpoint, the total drug exposure was 8658 PY
## Overall Summary of Safety

<table>
<thead>
<tr>
<th>Participants, %</th>
<th>DVY n=2694</th>
<th>TVD n=2693</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEs</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Grade ≥3 AEs</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Study-drug related AEs</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Grade ≥3 AEs</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>SAE</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Study-drug related SAEs</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>AEs leading to study drug discontinuation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Death&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

AE=adverse event; SAE=serious adverse event.

<sup>a</sup> 1 death due to traffic accident on DVY, 1 due to unknown reason in 26-year-old on TVD.
<table>
<thead>
<tr>
<th>Participants, %</th>
<th>DVY n=2694</th>
<th>TVD n=2693</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal chlamydia</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Oropharyngeal gonorrhea</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Rectal gonorrhea</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Exposure to communicable disease</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Syphilis</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Urethral chlamydia</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Gonorrhea and Chlamydia
3 Anatomic Site NAAT Testing by Study Visit

NAAT=nucleic acid amplification test.
Rectal Gonorrhea and Chlamydia
Rectal NAAT Testing by Study Visit

- DVY
- TVD

Week

Participants, %
## Concomitant Medications Used by >10% of Participants

<table>
<thead>
<tr>
<th>Drug</th>
<th>DVY n=2694</th>
<th>TVD n=2693</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Vitamins</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Benzathine benzylpenicillin</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>
## Common Study Drug-Related Adverse Events

≥1% in Either Arm

<table>
<thead>
<tr>
<th>Participants, %</th>
<th>DVY n=2694</th>
<th>TVD n=2693</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug-related AEs</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>&lt;1</td>
<td>1</td>
</tr>
</tbody>
</table>
## Select Grade ≥3 Laboratory Abnormalities

≥1% in Either Arm

<table>
<thead>
<tr>
<th>Participants, %</th>
<th>DVY n=2694</th>
<th>TVD n=2693</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ALT</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Amylase</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Serum glucose (nonfasting)</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>LDL (fasting)</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Urine glucose</td>
<td>&lt;1</td>
<td>1</td>
</tr>
</tbody>
</table>

ALT=alanine aminotransferase; AST=aspartate aminotransferase; LDL=low-density lipoprotein.
DISCOVER

Fasting Lipid Changes From Baseline at Week 48

<table>
<thead>
<tr>
<th></th>
<th>Total Cholesterol</th>
<th>LDL Cholesterol</th>
<th>HDL Cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVY</strong></td>
<td>-1</td>
<td>1</td>
<td>-2</td>
<td>4</td>
</tr>
<tr>
<td><strong>TVD</strong></td>
<td>-11</td>
<td>-7</td>
<td>-5</td>
<td>0</td>
</tr>
</tbody>
</table>

**Baseline, mg/dL:**
- Total Cholesterol: TVD 173, DVY 173
- LDL Cholesterol: TVD 99, DVY 100
- HDL Cholesterol: TVD 49, DVY 50
- Triglycerides: TVD 93, DVY 93

**Total Cholesterol:**
- TVD 3.4
- DVY 3.5

HDL=high-density lipoprotein.

p-values from 2-sided Wilcoxon rank sum test to compare treatment groups.
Renal Safety Assessment

- Clinical events
  - Proximal tubulopathy including Fanconi Syndrome
  - Renal AEs leading to discontinuation

- Glomerular function endpoints
  - Serum creatinine and estimated glomerular filtration rate $\text{Cockcroft-Gault}$
  - Total proteinuria (dipstick and UPCR)

- Proximal tubular function endpoints
  - Urine RBP:Cr
  - Urine β2M:Cr
Clinical Renal Events

- No cases of proximal tubulopathy in Descovy; one case of Fanconi syndrome in Truvada.
Glomerular Function: $e\text{GFR}_\text{CG}$

- DVY significantly improved median change from baseline in SCr compared with TVD ($p < 0.001$)

SCr = serum creatinine. $p$-values from Van Elteren test stratified by BL Truvada for PrEP to compare treatment groups.
Dipstick and Quantitative Proteinuria

BL=baseline.
p-values from rank analysis of covariance adjusting for BL category and BL Truvada for PrEP.
Proximal Tubular Proteinuria: RBP:Cr and β2M:Cr

- Median % Change From BL (Q1, Q3)
  - -60 to -30
  - 0
  - 30 to 60
  - 90
  - 120

- p-values from Van Elteren test stratified by baseline Truvada for PrEP to compare treatment groups.

- Urine RBP:Cr
  - DVY
  - TVD

- Urine β2M:Cr
  - p < 0.001

CC-73
Renal Safety Endpoints in Participants on Baseline Truvada

- DISCOVER trial included individuals using Truvada for PrEP and did not require washout prior to randomization (n=905)

- Prespecified safety analysis of current Truvada users who were randomized to Descovy
  - Significant improvements in glomerular and proximal tubular function observed
Glomerular Function: eGFR\textsubscript{CG} Participants on Baseline Truvada

- Baseline eGFR\textsubscript{CG}: DVY 119 mL/min, TVD 117 mL/min

p-value from 2-sided Wilcoxon rank sum test to compare treatment groups at Week 48.
Within participants on baseline TVD for PrEP, p <0.001 for all timepoints compared to baseline.
Proximal Tubular Function: RBP:Cr and β2M:Cr
Participants on Baseline Truvada

- Median % Change From BL (Q1, Q3)

Urine RBP:Cr

- DVY
- TVD

Urine β2M:Cr

p-values from Van Elteren test stratified by baseline Truvada for PrEP to compare treatment groups.

DISCOVER
Bone Safety at Week 48
Bone Mineral Density Substudy (n=383)

p-values from analysis of variance model with BL TVD for PrEP and treatment as fixed effects.
Spine Osteopenia and Osteoporosis
Bone Mineral Substudy (n=383)

Participants, %

<table>
<thead>
<tr>
<th></th>
<th>Descovy</th>
<th>Truvada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td>Week 48</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>n=190</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>n=159</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>n=188</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>n=160</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

BMD=bone mineral density.
p-value from rank analysis of covariance adjusting for BL BMD clinical status and BL TVD for PrEP to compare treatments.

DISCOVER
## Prespecified Secondary Safety Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Endpoints</th>
<th>Superior DVY</th>
<th>Superior TVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>% Change from baseline in hip BMD</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>% Change from baseline in spine BMD</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>% Change from baseline in urine β2M:Cr</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>% Change from baseline in urine RBP:Cr</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Distribution of UP and UPCR categories</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Change from baseline in serum creatinine</td>
<td>✔️</td>
<td></td>
</tr>
</tbody>
</table>
Descovy Safety Conclusions

- Low rates of SAEs and AEs leading to discontinuation
- DISCOVER results consistent with trials in HIV and HBV treatment
- DISCOVER confirmed Descovy’s superior safety
  - PrEP-naïve
  - Truvada switchers
Descovy for PrEP in Ciswomen and Adolescents
### Efficacy and Safety in HIV Treatment and Prevention

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prevention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TVD-based</strong> 15 m PY</td>
<td><strong>DVY-based</strong> 1.6 m PY</td>
<td><strong>TVD for PrEP 108,000 PY</strong></td>
</tr>
<tr>
<td><strong>DVY for PrEP 6,500 PY</strong></td>
<td><strong>Efficacy driven by tenofovir diphosphate in PBMCs</strong></td>
<td></td>
</tr>
<tr>
<td><strong>High virologic suppression</strong></td>
<td><strong>High virologic suppression</strong></td>
<td><strong>Low HIV incidence</strong></td>
</tr>
<tr>
<td><strong>Low HIV incidence</strong></td>
<td><strong>Safety driven by plasma tenofovir</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Bone and renal adverse effects</strong></td>
<td><strong>No bone and renal adverse effects</strong></td>
<td><strong>Bone and renal adverse effects</strong></td>
</tr>
<tr>
<td><strong>No bone and renal adverse effects</strong></td>
<td></td>
<td><strong>No bone and renal adverse effects</strong></td>
</tr>
</tbody>
</table>
PK is Independent of Intrinsic and Extrinsic Factors

PK of plasma TFV and TFV-DP in PBMCs is not affected by:
- Sex (male, female, intersex)
- Gender (cis, trans, genderqueer, nonbinary)
- Sexual orientation (straight, bisexual, pansexual, etc)
- Age
- HIV infection

PK=pharmacokinetics.
TFV-DP in PBMCs in DISCOVER, Cismen, and Ciswomen
Descovy and Truvada

Boxes show median (Q1, Q3); dots represent individual data in Q1, Q4. Data from cismen and ciswomen living with HIV.
HIV Treatment Efficacy in Women and Men

NON-DISCOVER: Phase 3 ARV-Naïve Trials of DVY- and TVD-based HIV Treatment

ARV=antiretroviral; VL=viral load.
NON-DISCOVER
Plasma TFV PK in Women With and Without HIV: $AUC_{\tau u}$
Descovy and Truvada

Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.

CC-86
Renal Safety in Women With HIV Through Week 96

NON-DISCOVER: Switching to DVY-based HIV Treatment

**Renal Safety in Women With HIV Through Week 96**

- **eGFR<sub>CG</sub>**
  - Median Change From BL, mL/min (Q1, Q3)
  - Week 0: -8, 0 (n=296), 8 (n=223)
  - Week 96: 8, 8 (n=296), 0 (n=223)
  - p <0.001

- **RBP:Cr**
  - Median % Change From BL (Q1, Q3)
  - Week 0: 0, 0 (n=296), 51 (n=223)
  - Week 96: 8, 8 (n=296), -10 (n=223)
  - p <0.001

- **β2M:Cr**
  - Median % Change From BL (Q1, Q3)
  - Week 0: 0, 0 (n=296), 29 (n=223)
  - Week 96: 10, 10 (n=296), -29 (n=223)
  - p <0.001
NON-DISCOVER: Pooled Analysis of Women in 4 Switch Studies in HIV Treatment

Spine Osteopenia and Osteoporosis in Women With HIV Through Week 48

p-value by rank analysis of covariance adjusting for baseline clinical status to compare treatments.
Descovy in Adolescents

- Descovy and three Descovy-containing single tablet regimens are approved for the treatment of HIV in adolescents weighing ≥35 kg
- Descovy has similar bone and renal safety benefits in adolescents with HIV
- Truvada was approved for PrEP in adolescents weighing ≥35 kg in 2018
TFV-DP in PBMCs in DISCOVER, Adults, and Adolescents: $C_{\text{tau}}$

Descovy and Truvada

Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.
HIV Treatment Efficacy in Adolescents

**Girls**
- n=28
- VL <50 c/mL: 93%
- VL ≥50 c/mL: 7%

**Boys**
- n=22
- VL <50 c/mL: 91%
- VL ≥50 c/mL: 9%
NON-DISCOVER: DVY- and TVD-based Treatment

Plasma TFV PK in Adults and Adolescents: $\text{AUC}_{\text{tau}}$

Descovy and Truvada

Boxes show median (Q1, Q3); dots represent individual data in Q1, Q4.

CC-92
Bone Safety in Adolescents With HIV Through Week 48

**NON-DISCOVER: ARV-Naïve Adolescents Who Initiated DVY-based Treatment (N=50)**

**Bone Densitometry (BMD) Median % Change From Baseline**

- **Week 0 to 48:**
  - Spine: +3.3%
  - Total Body (less head): +0.9%

**Legend:**
- Blue line: Spine
- Red line: Total Body

**Note:**
- Total body less head.

---

*CC-93*
Conclusions for Descovy in Ciswomen and Adolescents

- Descovy is noninferior to Truvada in HIV treatment and prevention efficacy
  - Tenofovir diphosphate levels in PBMCs are comparable in the men and transwomen in DISCOVER, in ciswomen, and in adolescents

- Descovy is superior to Truvada in renal and bone safety—relevant for women and adolescents
  - Plasma tenofovir is 90% lower with Descovy than Truvada and comparably low in DISCOVER, ciswomen, and adolescents

- Data support the inclusive indication
Future Studies
Studying Descovy for PrEP in Ciswomen and Adolescents

- Ciswomen not included in DISCOVER
  - HIV incidence is 13-fold lower for US women vs MSM at high risk for HIV
- Placebo-controlled trial not ethical
  - Truvada efficacy established in adherent women
- Superiority to Truvada trial not appropriate
  - Oral daily pills differentiated primarily on safety
- Dedicated NI trial in women has considerable statistical design challenges: N=22,000, ~8–10 years to conduct
- DISCOVER design not optimized for adolescents
## Selected PrEP Effectiveness Studies for Descovy

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Sample Size</th>
<th>Participants</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP Vacc</td>
<td>N~1688</td>
<td>Women &amp; men</td>
<td>South Africa</td>
</tr>
<tr>
<td>Descovy for PrEP</td>
<td>N~525</td>
<td>Women &amp; men</td>
<td>US &amp; Sub-Saharan Africa</td>
</tr>
<tr>
<td>Descovy for PrEP</td>
<td>N=500</td>
<td>Adolescents, women &amp; men</td>
<td>Rural Kenya and Uganda</td>
</tr>
<tr>
<td>DVY for PrEP in Pregnancy</td>
<td>N~360</td>
<td>Pregnant &amp; breastfeeding women</td>
<td>Kampala, Uganda</td>
</tr>
<tr>
<td>YW Telehealth</td>
<td>N=100</td>
<td>Black cis- &amp; transwomen</td>
<td>Birmingham, AL</td>
</tr>
<tr>
<td>Rapid PrEP</td>
<td>N=290</td>
<td>Black adolescent MSM</td>
<td>16–24 y Southern US</td>
</tr>
</tbody>
</table>
Clinical Context

Richard Elion, MD

Director of Research
Washington Health Institute
Clinical Professor of Medicine
George Washington University
Current HIV Treatment Coverage Is Not Enough to Prevent New HIV Transmission

8.5% persons with HIV who are engaged in care

Persons diagnosed with HIV but not retained in care

Persons with HIV but undiagnosed

Unmet Need: 91.5%

HIV Prevention Strategies

- Condoms
- PEP
- Voluntary Male Circumcision
- Needle Exchange
- Vaccine
- Abstinence
- HIV Treatment
- PrEP
- Microbicides
- HIV & STI Testing
- STI Treatment
- Harm Reduction
HIV Prevention Strategies

- Biomedical interventions, including TasP and PrEP, are among the most useful

States Grouped by PrEP Use

Low: 13–42/100K; Medium low: 42–53/100K; Medium: 53–61/100K; Medium high: 62–78/100K; High: 81–178/100K.

PrEP Use in Communities in Need


Descovy for PrEP for Adolescents

- Truvada for PrEP efficacious in adolescents
- HIV infection and prevention biology consistent across ages
- Descovy data support use with adolescents
  - Descovy for treatment efficacious in adolescents
  - Descovy for PrEP efficacious in cismen and transgender women
  - Descovy pharmacology consistent across ages
- Important option for adolescents
  - Deposit bone through mid-thirties
Adolescents: Value of Z scores (Age-adjusted)
On and off Truvada for PrEP

*p ≤0.05 for change from baseline by paired t-test; Havens PL. Clin Infect Dis 2019 [in press]. EPH=extension phase out through 96 additional weeks of follow from either Week 48 or a positive HIV diagnosis.
Potential PK Advantages

- TAF leads to lower plasma TFV levels resulting in reduced off-target side effects.
- TAF rapidly leads to higher TFV-DP in PBMCs resulting in increased antiviral effect and potential efficacy advantage.
  - The TFV-DP PK advantages represent a potential forgiveness advantage if adherence is imperfect.
- These PK advantages may be beneficial for prevention.
Efficacy of Truvada for PrEP in Women

- Partners PrEP and TDF2 reflected efficacy in women when adherence was comparable to other studies.
- VOICE and FEM-PrEP showed poor efficacy when adherence was equally deficient.
Women and PrEP

- 93% of HIV-negative women reported having vaginal sex without a condom in the previous year
- 26% reported having anal sex without a condom

Of the >170,000 women at risk, only 2% have started Truvada for PrEP

HIV Incidence
HIV Seroconversion Across 46 TVD for PrEP Demonstration Projects

Real world data on TVD PrEP use from 46 demo projects in nearly 10,000 men and women

HIV Incidence Rate, per 100 PY (95% CI)

- Overall: 0.64 (n=10,609, 64 infections in 9936 PY)
- Men: 0.64 (n=8047, 54 infections in 8385 PY)
- Women: 0.81 (n=2133, 9 infections in 1114 PY)

Reasons for Lack of Willingness to Use PrEP

- I'm not at risk for HIV infection: 65% (Total), 73% (High risk), 88% (Low risk), 77% (MSM)
- I don't believe it would actually work: 29% (Total), 28% (High risk), 28% (Low risk), 14% (MSM)
- I'm afraid of potential side effects: 26% (Total), 15% (High risk), 18% (Low risk), 15% (MSM)
- I don't like taking pills daily: 18% (Total), 10% (High risk), 15% (Low risk), 15% (MSM)
- I would not want to pay for it: 13% (Total), 5% (High risk), 3% (Low risk), 3% (MSM)
- I'm afraid that someone would find out I was taking it: 1% (Total), 1% (High risk), 1% (Low risk), 0% (MSM)

Survey Participants, %

Women: Descovy Bone Safety Data

- Truvada-based regimens are associated with declines in bone mineral density\(^1\)
- Increased risk of fracture in people living with HIV who have taken Truvada-based regimens\(^2\)
- Descovy-based regimens are not associated with declines in bone mineral density

Descovy for PrEP for Cis Women

- Truvada for PrEP is equally effective in men and women when controlling for adherence as seen in clinical trials (Partner’s PrEP, TDF2, and Bangkok, as well as demonstration projects)
- PBMC drug levels are associated with efficacy for HIV prevention
  - HIV is a systemic disease
  - Drug levels in PBMCs correlate with efficacy in treatment and prevention
- PBMC drug levels for Descovy are similar between men and women
  - Higher than with Truvada
- Descovy will be effective for PrEP in cis-women
Conclusions

- PrEP is a key tool in the ongoing fight to end the HIV epidemic
- Descovy is a safer, well tolerated and effective treatment for PrEP
  - Improved bone and renal safety
  - At least as effective as Truvada
- Evidence supports extrapolation to ciswomen and adolescents
- The benefit:risk profile of Descovy for HIV prevention supports making this drug available to all those in need
Backup Slides Shown
Bone Mineral Density and Bone Adverse Events

**Hip BMD**

- DVY-based regimen
- TVD-based regimen

<table>
<thead>
<tr>
<th>Week</th>
<th>DVY-based</th>
<th>TVD-based</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.4</td>
<td>-1.7</td>
</tr>
<tr>
<td>24</td>
<td>-0.7</td>
<td>-2.9</td>
</tr>
<tr>
<td>48</td>
<td>-0.6</td>
<td>-3.3</td>
</tr>
<tr>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>-0.8</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

Mean % Change From BL:
- p <0.001 for all visits

**Bone AE Discontinuations**

<table>
<thead>
<tr>
<th>Week</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>96</td>
<td>3</td>
</tr>
<tr>
<td>144</td>
<td>6</td>
</tr>
</tbody>
</table>

AE=adverse event; BMD=bone mineral density.
TDF Use and Fracture Risk

- Analysis from the EuroSIDA cohort, with 619 fractures in 86,118 PY of follow-up
- Multivariate analysis of fracture risk adjusted for demographics, HIV-specific variables, and comorbidities

- TDF: ever vs never
  - 1.40 (1.15, 1.70)

- TDF: on vs off
  - 1.25 (1.05, 1.49)

CI=confidence interval; PY=person-year; TDF=tenofovir disoproxil fumarate.
# TDF and Truvada PrEP With Trend Towards Increased Fractures

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study or subgroup</th>
<th>Risk Ratio (95% CI)</th>
<th>Favors PrEP</th>
<th>Favors PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TDF</strong></td>
<td>Bangkok TFV Study</td>
<td>1.29 (0.96, 1.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDC Safety Study&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.98 (0.50, 7.81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partners PrEP: TDF arm</td>
<td>0.92 (0.34, 2.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VOICE: TDF arm</td>
<td>2.51 (0.12, 52.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td>1.29 (0.98, 1.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TVD</strong></td>
<td>IPERGAY&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.51 (0.13, 1.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>iPrEx</td>
<td>1.36 (0.63, 2.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partners PrEP: TVD arm</td>
<td>0.75 (0.27, 2.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PROUD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.93 (0.31, 28.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF2</td>
<td>1.16 (0.39, 3.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VOICE: TVD arm&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.51 (0.06, 36.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td>1.06 (0.66, 1.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td>1.23 (0.97, 1.56)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI=confidence interval; TDF=tenofovir disoproxil fumarate; TFV=tenofovir.

<sup>a</sup> US, Canada, or Europe; <sup>b</sup> Lower limb fracture. Area of each circle represents weight given to study in meta-analysis. Area of diamond represents sample size for pooled estimate; width of diamond represents CI for pooled estimate. Chou R, JAMA 2019;321:2214-30.
Renal Discontinuation and Renal Tubular Biomarkers

Renal AE Discontinuations

<table>
<thead>
<tr>
<th>Weeks</th>
<th>DVY-based regimen</th>
<th>TVD-based regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>96</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>144</td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>

Median % Change (IQR)

β2M:Cr

p <0.001 for all visits

Participants, n

AE=adverse event; β2M:Cr=β2-microglobulin:creatinine; IQR=interquartile range.
## Truvada PrEP associated with Increased Risk of Renal AEs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study or subgroup</th>
<th>Risk Ratio (95% CI)</th>
<th>Favors PrEP</th>
<th>Favors PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TDF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bangkok TFV Study</td>
<td>1.36 (0.86, 2.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDC Safety Study(^{a,b})</td>
<td>0.20 (0.01, 4.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partners PrEP: TDF arm</td>
<td>1.58 (0.63, 3.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study of TDF</td>
<td>0.88 (0.42, 1.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VOICE: TDF arm(^c)</td>
<td>2.01 (0.22, 17.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td>1.24 (0.87, 1.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TVD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEM-PrEP</td>
<td>1.30 (0.92, 1.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IAVI Kenya Study</td>
<td>3.57 (0.19, 66.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IAVI Uganda Study</td>
<td>2.55 (0.13, 51.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IPERGAY(^a)</td>
<td>1.77 (1.06, 2.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>iPrEx</td>
<td>1.78 (0.93, 3.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partners PrEP: TVD arm</td>
<td>1.43 (0.61, 3.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PROUD(^a,d)</td>
<td>6.85 (0.36, 131.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF2</td>
<td>2.99 (0.12, 73.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VOICE: TVD arm(^e)</td>
<td>6.53 (0.86, 49.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td>1.54 (1.21, 1.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>1.43 (1.18, 1.75)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE=adverse event; CI=confidence interval; Cr=creatinine; TDF=tenofovir disoproxil fumarate; TFV=tenofovir. \(^a\) U.S, Canada, or Europe; \(^b\) Cr elevation leading to study withdrawal; \(^c\) Any Cr event; \(^d\) Study drug interruption due to high Cr concentration; \(^e\) Any Cr event. Area of each circle represents weight given to study in meta-analysis. Area of diamond represents sample size for pooled estimate; width of diamond represents CI for pooled estimate. Chou R, JAMA 2019;321:2214-30.
PrEP Adherence Correlates with Efficacy in Previous Trials

TFV = tenofovir.
* TFV “Detected” in Plasma Samples in Active Arm or >90% by Self-report/pill Count/refill Records
**PrEP is Highly Effective in MSM, Heterosexual Men and Women**

**CDC PrEP Guidance**


† The guidelines for PrEP use in the U.S. recommends daily oral PrEP and daily dosing is the only FDA-approved schedule for taking PrEP to prevent HIV.

“Optimal use” is defined as taking PrEP daily, “Consistent use” is defined as taking PrEP at least 4 pills/week

“Recent use” of oral PrEP is determined by detecting any amount of TFV in plasma.

---

### Oral Daily Pre-Exposure Prophylaxis (PrEP)† for HIV-Negative Persons

<table>
<thead>
<tr>
<th>Population</th>
<th>Effectiveness Estimate</th>
<th>Source</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men who have sex with men (MSM)</td>
<td>~99%</td>
<td>Grant, 2014, Liu, 2015, McCormack, 2015, Volk, 2015, Marcus, 2017</td>
<td>When taking PrEP daily or consistently (at least 4 times per week), the risk of acquiring HIV is reduced by about 99% among MSM. While daily use is recommended in the U.S., taking PrEP consistently (at least 4 times per week) appears to provide similar levels of protection among MSM. The effectiveness of oral PrEP is highly dependent on PrEP adherence. When taking oral PrEP daily or consistently, HIV acquisition is extremely rare and has not been observed in any of the studies described below. In clinical practice, a few cases of new HIV infections have been confirmed while HIV-negative individuals were on PrEP with verified adherence.</td>
</tr>
<tr>
<td>Heterosexual Men and Women</td>
<td>~99%</td>
<td>N/A</td>
<td>There is evidence for the effectiveness of PrEP when used recently ² (based on detecting TFV in plasma), which is estimated to be 88 – 90% as described below. There is no effectiveness estimate of PrEP when taken daily or consistently among heterosexuals; however, it is likely to be greater than the estimates corresponding to recent use and similar to what has been observed for MSM. The effectiveness of oral daily PrEP is highly dependent on PrEP adherence, with maximum effectiveness when taking PrEP daily and lower effectiveness when not taken consistently.</td>
</tr>
</tbody>
</table>

---


† The guidelines for PrEP use in the U.S. recommends daily oral PrEP and daily dosing is the only FDA-approved schedule for taking PrEP to prevent HIV.

“Optimal use” is defined as taking PrEP daily, “Consistent use” is defined as taking PrEP at least 4 pills/week

“Recent use” of oral PrEP is determined by detecting any amount of TFV in plasma.
NON-DISCOVER: ARV-Naïve Adolescents Who Initiated DVY-based Treatment (N=50)

Bone Safety in Adolescents With HIV

HA=height-adjusted; Q=quartile; TBLH=total body less head.
Spine and Hip BMD at Week 48
Age <25 and ≥25 y

BMD=bone mineral density; SEM=standard error of the mean.

p-values from analysis of variance model including baseline TVD for PrEP and treatment as fixed effects.

BMD=bone mineral density; SEM=standard error of the mean.

p-values from analysis of variance model including baseline TVD for PrEP and treatment as fixed effects.
PrEP is Highly Effective in MSM, Heterosexual Men and Women

Evidence supporting CDC PrEP Guidance¹

- Case-control study of Partners PrEP²
  - Risk reduction in participants with detectable plasma TFV for the visit at which HIV was diagnosed was 90%

- Gender-specific case-control study of Partners PrEP³
  - Risk reduction for participants taking Truvada with detectable TFV levels:
    - All: 92%
    - Men: 89%
    - Women: 94%

- Both the original analysis and the gender-specific sub-analysis concluded that PrEP was similarly effective in men and women

NON-DISCOVER: Young African Women on PrEP

PrEP Efficacy in Women: HPTN 082

400 women aged 16–25 years
- South Africa and Zimbabwe
- HIV incidence = 1.0 per 100 PY (95% CI 0.3, 2.5)

<table>
<thead>
<tr>
<th>Adherence, DBS</th>
<th>HIV Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4 doses/wk</td>
<td>0</td>
</tr>
<tr>
<td>2–3 doses/wk</td>
<td>0</td>
</tr>
<tr>
<td>&lt;2 doses/wk</td>
<td>2</td>
</tr>
<tr>
<td>BLQ TFV-DP</td>
<td>2</td>
</tr>
</tbody>
</table>

BLQ=below the level of quantitation; CI=confidence interval; DBS=dried blood spot; PY=person-years; TFV-DP=tenofovir diphosphate.
TFV-DP in Vaginal and Rectal Tissue With Truvada

C₄h=concentration at 4 h; IQR=interquartile range; TFV-DP=tenofovir diphosphate. Boxes depict median (IQR); whiskers depict min, max.

a. 1 vaginal sample collected 4h postdose; 40% TVD samples quantifiable in vaginal tissues.

b. 4 different rectal samples collected for each participant 4h postdose; 96% TVD samples quantifiable in rectal tissues.

TFV-DP in Vaginal and Rectal Tissue: \(C_{4h}\)

Vaginal\(^a\)

- **DVY**: n=6
- **TVD**: n=5

Rectal\(^b\)

- **DVY**: n=7
- **TVD**: n=7

\[C_{4h}= \text{concentration at 4 h; IQR=interquartile range; TFV-DP=tenofovir diphosphate. Boxes depict median (IQR); whiskers depict min, max.}\]

\(^a\) 1 vaginal sample collected 4h postdose; 100% DVY samples quantifiable; 40% TVD samples quantifiable in vaginal tissues.

\(^b\) 4 different rectal samples collected for each participant 4h postdose; 71% DVY samples quantifiable; 96% TVD samples quantifiable in rectal tissues.

TFV-DP is an Adherence Biomarker in DBS

TFV-DP Half Life in RBC ~17–20 days

- DBS provides an objective measure of average adherence during the prior ~8 weeks

DBS=dried blood spot; RBC=red blood cell; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; TFV-DP=tenofovir diphosphate.
Castillo-Mancilla, J. 2012 AHRH.
Determination of TFV-DP Level and Adherence by DBS

DBS=dropped blood spot; LC-MS/MS=liquid chromatography–tandem mass spectrometry; RBC=red blood cell; TFV-DP=tenofovir-diphosphate.
iPrEx OLE: DBS Thresholds and HIV Risk Reduction With Truvada

Adherence

- <2 Tablets/wk
- 2–3 Tablets/wk
- ≥4 Tablets/wk

<table>
<thead>
<tr>
<th>Adherence</th>
<th>HIV Incidence Rate, per 100 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 Tablets/wk</td>
<td>5 LLOQ</td>
</tr>
<tr>
<td>2–3 Tablets/wk</td>
<td>4 Off PrEP</td>
</tr>
<tr>
<td>≥4 Tablets/wk</td>
<td>3 Truvada</td>
</tr>
</tbody>
</table>

- 86% RR (95% CI 21, 99)
- 100% RR (95% CI 86, 100)

TFV-DP, fmol/punch

CI=confidence interval; DBS=dried blood spot; LLOQ=lower limit of quantitation; PY=person-year; RR=risk reduction; TFV-DP=tenofovir diphosphate.

PBMC TFV-DP Levels and Protection From HIV With Truvada

EC₉₀ Established From iPrEx Case-Control; Dosing from STRAND

- Adherence: 2 doses/wk ≥4 doses/wk
  - Adherence: 76% (CI 56, 96)
  - Adherence: ≥96% (CI 90, >99)

- Risk Reduction: 
  - Placebo: HIV Incidence Rate, per 100 PY (iPrEx)
  - Truvada: 90% risk reduction

TFV-DP, fmol/10⁶ PBMCs

CI=confidence interval; EC₉₀=90% effective concentration; PBMC=peripheral blood mononuclear cell; PY=person-year; TFV-DP=tenofovir-diphosphate.

Descovy and Truvada achieve comparable TFV-DP levels in vaginal tissue:

- Single dose Descovy and Truvada cross-study comparison
- Single dose Descovy and Truvada within-study comparison
- Multiple dose Descovy and Truvada within-study comparison
Vaginal TFV-DP Tissue Levels With Descovy and Truvada

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>TVD</th>
<th>DVY</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-48h}$</td>
<td>170,674</td>
<td>132,098</td>
<td>1.3$^1$ to 1.8-fold$^2$ lower with DVY</td>
</tr>
<tr>
<td><strong>Single dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_{4h}$</td>
<td>100% BLQ</td>
<td>69% BLQ</td>
<td>Multiple dose data needed</td>
</tr>
<tr>
<td>C$_{24h}$</td>
<td>57,450</td>
<td>151,000</td>
<td>2.6-fold higher with DVY</td>
</tr>
<tr>
<td><strong>Multiple dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_{24h}$</td>
<td>69% BLQ</td>
<td>80% BLQ</td>
<td>Comparable and low levels with DVY and TVD</td>
</tr>
<tr>
<td>C$_{48h}$</td>
<td>75% BLQ</td>
<td>80% BLQ</td>
<td></td>
</tr>
</tbody>
</table>

AUC$_{0-48h}$ = area under curve from time 0 to 48 h; C$_{xh}$ = concentration at X h; BLQ = below limit of quantification; TFV-DP = tenofovir-diphosphate.  

a. h·fmol/g; b. fmol/g.

## Methods to Measure TFV-DP Levels in Tissue

<table>
<thead>
<tr>
<th>Tissue Sampling</th>
<th>Homogenization of Tissue</th>
<th>TFV-DP Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic or vaginal tissue collected using pinch biopsy forceps</td>
<td>Biopsies incubated with enzymes to break up cells and tissue</td>
<td>TFV-DP, TFV-MP and TFV present in cell lysates analyzed with a LC-MS/MS mass spectrometer</td>
</tr>
</tbody>
</table>

Epithelial cells  
Fibroblasts  
Macrophages  
T cells  
B cells  
Neutrophils  
NK cells  
Dendritic cells  

LC-MS/MS=liquid chromatography-tandem mass spectrometry; NK=natural killer; TFV-D/MP=tenofovir di/monophosphate.

**TFV-DP in PBMCs in MSM and TGW on High-dose Hormones Descovy**

**C_{tau}** = trough concentration; MSM = men who have sex with men; PBMC = peripheral blood mononuclear cell; Q = quartile; TFV-DP = tenofovir-diphosphate; TGW = transgender women.

Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.
### Condomless Insertive Anal Intercourse Partners

#### Number in the 90 Days Prior to Screening

<table>
<thead>
<tr>
<th></th>
<th>DVY (n=2602)</th>
<th>TVD (n=2597)</th>
<th>Total (n=5199)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>4 (6.8)</td>
<td>4 (7.3)</td>
<td>4 (7.0)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>2 (1, 5)</td>
<td>2 (1, 4)</td>
<td>2 (1, 5)</td>
</tr>
<tr>
<td>Partners, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>495 (19)</td>
<td>534 (21)</td>
<td>1029 (20)</td>
</tr>
<tr>
<td>1</td>
<td>455 (17)</td>
<td>453 (17)</td>
<td>908 (17)</td>
</tr>
<tr>
<td>2</td>
<td>490 (19)</td>
<td>489 (19)</td>
<td>979 (19)</td>
</tr>
<tr>
<td>3</td>
<td>325 (12)</td>
<td>315 (12)</td>
<td>640 (12)</td>
</tr>
<tr>
<td>4–5</td>
<td>305 (12)</td>
<td>315 (12)</td>
<td>620 (12)</td>
</tr>
<tr>
<td>6–10</td>
<td>320 (12)</td>
<td>294 (11)</td>
<td>614 (12)</td>
</tr>
<tr>
<td>≥11</td>
<td>212 (8)</td>
<td>197 (8)</td>
<td>409 (8)</td>
</tr>
<tr>
<td>Missing</td>
<td>92</td>
<td>96</td>
<td>188</td>
</tr>
</tbody>
</table>

Q=quartile; SD=standard deviation.

Missing categories were excluded from % calculation; CASI questionnaires from screening visit.
Women’s Study Sample Size Calculations in US and High-Incidence Settings

- **US**: incidence in high risk women = 0.32/100 PY
- **Africa**: incidence in high risk women in 2019 = 4/100 PY
- Based on Partners PrEP and Bangkok Tenofovir Study, NI margin = 1.27 (to preserve 50% effect)

<table>
<thead>
<tr>
<th>Study</th>
<th>TVD Incidence rate, per 100 PY</th>
<th>IRR, D Vy to TVD</th>
<th>Test</th>
<th>Power</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>US women</td>
<td>0.10</td>
<td>1</td>
<td>Noninferiority test, margin 1.27</td>
<td>80%</td>
<td>275,000</td>
</tr>
<tr>
<td>African women High-incidence</td>
<td>1.25</td>
<td>1</td>
<td>Noninferiority test, margin 1.27</td>
<td>80%</td>
<td>22,000</td>
</tr>
</tbody>
</table>

IDU=injecting drug users; IRR=incidence rate ratio; MSM=men who have sex with men; PY=person-year; RR=rate ratio.
Estimated Placebo Rate for New HIV Cases by Site

<table>
<thead>
<tr>
<th>Year</th>
<th>HIV Incidence Rate, per 100 PY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>4.86 (4.73, 5.00)</td>
</tr>
<tr>
<td>2013</td>
<td>4.69 (4.56, 4.82)</td>
</tr>
<tr>
<td>2014</td>
<td>4.24 (4.08, 4.40)</td>
</tr>
<tr>
<td>2015</td>
<td>3.80 (3.64, 3.96)</td>
</tr>
<tr>
<td>2016</td>
<td>3.82 (3.67, 4.00)</td>
</tr>
<tr>
<td>2017</td>
<td>3.61 (3.45, 3.77)</td>
</tr>
</tbody>
</table>

CI=confidence interval; MSA=metropolitan statistical area; PY=person-years.
CDC-defined persons with an indication for PrEP use (Smith Ann Epidemiol 2018); Mera JIAS 2019, under review.
DISCOVER Study and Truvada for PrEP Use
US Race and Ethnicity

Mullick and Murray\(^1\) analyzed MSM RG incidence and HIV incidence in several cohort studies (not on PrEP), concluded that the observed RG rate could be used to predict the expected HIV incidence rate in PrEP studies.

MSM=men who have sex with men; PY=person-year; RG=rectal gonorrhea.

Observed Rates Compared to Historic Rates

- Primary analysis: the observed incidence rate ratio = 0.47 (95% CI 0.19, 1.15)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Source</th>
<th>HIV Incidence Rate, per 100 PY</th>
<th>Incidence Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol (2016)</td>
<td>3 reference CTs: iPrEX (URAI)(^1), PROUD(^2), IPERGAY(^3)</td>
<td>PBO=6.96</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TVD=1.44</td>
<td></td>
</tr>
<tr>
<td>Epi (CDC) &amp; DISCOVER</td>
<td>Mera et al (2019)(^4)</td>
<td>PBO=3.83</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>DISCOVER study (US)</td>
<td>TVD=0.446</td>
<td></td>
</tr>
<tr>
<td>rGC Correlate &amp; DISCOVER</td>
<td>Mullick &amp; Murray (2019)(^5)</td>
<td>PBO=6.36</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>DISCOVER study</td>
<td>TVD=0.342</td>
<td></td>
</tr>
</tbody>
</table>

CI=confidence interval; MSM=men who have sex with men; URAI=Unprotected Receptive Anal Intercourse; rGC=rectal gonorrhea.
Adherence by Pill Counts: Age Subgroups

Participants, %

Age <25 y  
- ≥95: 52
- ≥80–<95: 36
- <80: 12
  n=629

Age ≥25–<50 y  
- ≥95: 69
- ≥80–<95: 24
- <80: 7
  n=4042

Age ≥50 y  
- ≥95: 80
- ≥80–<95: 16
- <80: 5
  n=716
Weight Gain in PrEP Trials

Adherence by DBS: Age Subgroups

- **Age <25 y**
  - n=47
  - Adherence:
    - Week 12: 91%
    - Week 24: 93%
    - Week 36: 81%
    - Week 48: 79%
    - Week 60: 80%
    - Week 72: 72%
    - Week 84: 74%
    - Week 96: 69%

- **Age ≥25–<50 y**
  - n=408
  - Adherence:
    - Week 12: 95%
    - Week 24: 90%
    - Week 36: 91%
    - Week 48: 91%
    - Week 60: 88%
    - Week 72: 89%
    - Week 84: 88%
    - Week 96: 86%

- **Age ≥50 y**
  - n=81
  - Adherence:
    - Week 12: 95%
    - Week 24: 96%
    - Week 36: 95%
    - Week 48: 89%
    - Week 60: 90%
    - Week 72: 92%
    - Week 84: 89%
    - Week 96: 87%
HIV Incidence Predicted by Rectal Gonorrhea Rate

Mullick and Murray\(^1\) analyzed MSM rectal GC incidence and HIV incidence in 8 cohort studies (not on PrEP).

Concluded that observed rectal GC rate could be used to predict the expected HIV incidence rate in PrEP studies.

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Cl=confidence interval; GC=gonococcal proctitis; MSM=men who have sex with men; PY=person-years.