NDA 208215/S-012

DESCOVY®

(emtricitabine 200 mg/tenofovir alafenamide 25 mg)

Pre-exposure Prophylaxis (PrEP) Indication for Prevention of Sexually-Acquired HIV-1 Infection

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING
August 7, 2019

Jeffrey Murray, MD, MPH – Deputy Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

2012 7 years 2019

HIV Treatment ✓
HIV Prevention ✓

HIV Treatment ✓
HIV Prevention ?

HIV Prevention
Drug Development Caveat

The Development Approach of Descovy ® emtricitabine/tenofovir alafenamide (F/TAF)

for HIV PrEP May Not Apply to Future New Molecular Entities Because a Pro-Drug of TFV for PrEP Has Been Previously Approved

Regulatory Considerations

Number of Clinical Trials

- For a new molecule: generally two trials
- For a new related indicated: often one trial
- For a new dosing schedule (twice to once daily): mostly one trial
- For a new population where PK is different: one trial

NDA 208215/S-012
DESCOVY® for PrEP

- Initial Drug Development Advice:
  - Clinical trials in relevant populations recommended
  - PK link, alone, not possible
- One clinical trial completed (men who have sex with men/transgender women) (MSM/TGW)
- Given uncertainty around the protective correlate, can extrapolation be used to further expand the indicated population?

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August 7, 2019

Peter Miele, MD - Medical Officer
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Agenda

- Proposed Indication
- Background
  - Role of Mucosal Tissue Drug Concentrations in HIV Prevention
- DISCOVER Trial in Men and Transgender Women Who Have Sex with Men
  - Efficacy
  - Safety
- Extrapolation Approach to Support Indication in Cisgender Women
  - Study A15-137

NDA 208215/S-012

Application proposes new indication for Descovy®
(emtricitabine 200 mg/tenofovir alafenamide 25 mg, F/TAF):

Pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg

NDA 208215/S-012

Proposed PrEP indication would apply to adult and adolescent:

- men and transgender women who have sex with men (MSM/TGW)
- men who have sex with women
- cisgender women who have sex with men

Proposed indication is similar to current PrEP indication for Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, F/TDF)

Background: TRUVADA® for PrEP

- Approved labeled indication:
  - *TRUVADA® is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg*

- Data to support PrEP indication for Truvada®:
  - Phase 3 double-blind, placebo-controlled RCT in adult MSM/TGW (iPrEx)
  - Phase 3 double-blind, placebo-controlled RCT in adult heterosexual men and women in HIV serodiscordant relationships (Partners PrEP)
  - Phase 2 open-label trial in adolescent MSM (ATN 113)

RCT=randomized clinical trial

Background: TAF vs. TDF

- Both approved for treatment of HIV-1 and HBV
- Compared to TDF 300 mg, oral administration of TAF 25 mg results in:
  - 4-7-fold higher intracellular levels of active metabolite tenofovir diphosphate (TFV-DP) in PBMCs
  - 90% lower plasma levels of tenofovir (TVF)
- Differences in TFV plasma exposure may explain differences in safety profile between TAF and TDF

PBMC = peripheral blood mononuclear cell

Background: TAF vs. TDF

- Published single-dose PK studies suggest that 25 mg oral TAF achieves lower TFV and TFV-DP levels in rectal and vaginal mucosal tissues (homogenates) compared with oral 300 mg TDF

Cottrell M, et al. J Infect Dis 2016; 214: 55-64
Cottrell M, et al. J Antimicrob Chemother 2017; 72: 1731-40

Background: Use of Antiretroviral Drugs for HIV Prevention

- The relative importance of mucosal tissue vs. systemic drug concentrations to PrEP efficacy is unknown

- The minimum drug concentration in mucosal tissues (if relevant) that would be considered protective against HIV-1 infection is unknown

Role of Mucosal Tissue Drug Exposure in PrEP Efficacy?

- Topical microbicide experience
  - Vaginal mucosal tissue drug concentrations, with very limited systemic exposure, can reduce the risk of HIV-1 infection
- Oral TDF dosing results in lower TFV-DP exposure in vaginal tissue vs. rectal tissue
  - Concerns have been raised that poor adherence plus differential drug distribution may have contributed to mixed efficacy results in PrEP trials of F/TDF in cisgender women vs. MSM

Patterson K, et al. Sci Transl Med 2011; 3:112re4; Thigpen M, et al. N Engl J Med 2012: 376:423-34; Van Damme, L et al. N Eng J Med 2012; 367:411-22; Louissaint N, et al. AIDS Res Hum Retroviruses 2013; 29:1443-50; Marrazzo, J et al. N Eng J Med 2015; 372:509-18; Cottrell M, et al. J Infect Dis 2016; 214:55-64; Anderson P, et al. Curr Opin HIV AIDS 2016; 11:94-101; Seiffert S, et al. AIDS Res Hum Retroviruses 2016; 32:981-91

Role of Mucosal Tissue Drug Exposure in PrEP Efficacy?

- Current CDC PrEP guidelines for F/TDF acknowledge lack of scientific consensus on protective contribution of drug exposure in specific body tissues
  - CDC reports time to achieve *maximum* intracellular concentrations of TFV-DP in PBMCs (20 days), rectal tissue (7 days), and cervicovaginal tissue (20 days) based on PK studies
- Some state guidelines also recognize the tissue differential in discussing time to achieve "protective concentrations"
  - 7 days of daily PrEP use for protection with receptive anal sex
  - 20 days of daily PrEP use for protection with receptive vaginal sex

CDC 2017; New York State Department of Health AIDS Institute 2017

Background: F/TAF for PrEP

Given:

- Lack of consensus regarding contribution of local tissue vs. systemic drug exposure to PrEP efficacy
- Reports of lower mucosal tissue TFV-DP concentrations with oral TAF vs. TDF dosing

FDA determined that fully-powered clinical trials would be needed to support efficacy of F/TAF for PrEP, using F/TDF as an active control

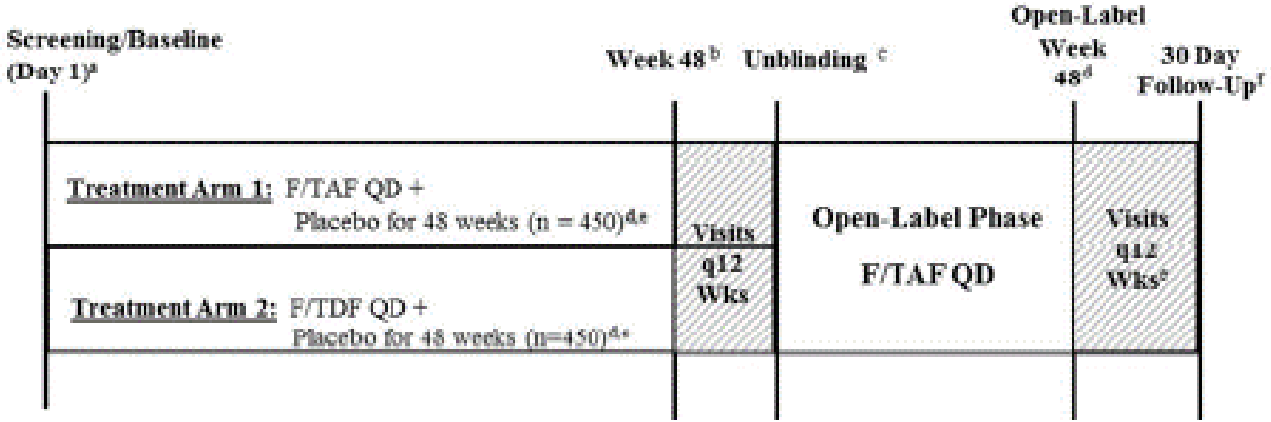
NDA 208215/S-012

- Data submitted to support a PrEP indication for Descovy®:
  - one Phase 3 double-blind, active-controlled RCT in MSM/TGW (DISCOVER)

- To support an indication in cisgender women and adolescents, an extrapolation approach is proposed

DISCOVER Study Design

- Double-blind, non-inferiority trial of 5,000 subjects randomized to F/TAF or F/TDF for at least 96 Weeks
- Following the Day 1 visit, subjects returned for study visits at Weeks 4 and 12, and then every 12 weeks thereafter



Source: Protocol GS-US-412-2055

DISCOVER Study Design

Primary Efficacy Endpoint:

- The incidence of HIV-1 infections per 100 person-years (PY) when all subjects had reached a minimum of 48 weeks of follow-up and at least 50% had 96 weeks of follow-up or were permanently discontinued from the trial

DISCOVER Study Design

- For the relative risk analysis, a noninferiority margin of **1.62** per 100 PY was derived based on historical data from three clinical trials of F/TDF for PrEP in MSM (i.e., iPrEx, PROUD, IPERGAY)

Clinical Trial	Sample Size Placebo (PY Follow-Up)	Sample Size F/TDF (PY Follow-Up)	Seroconversions (Incidence per 100 PY [95% CI])		Rate Ratios in Seroconversion Rates, per 100 PY [95% CI]	Enrolment
			PBO	F/TDF		
IPREX (URAI subgroup) at screening	753 (1054)	732 (1055)	56 (5.3) [4.0, 6.8]	23 (2.2) [1.4, 3.2]	2.4 [1.5, 3.9]	July 10, 2007 - Dec 17, 2009
PROUD	255 (222)	268 (243)	20 (9.0) [5.6, 13.4]	3 (1.2) [0.3, 3.5]	7.3 [2.2, 24.2]	Nov 29, 2012 – Apr 30, 2014
IPERGAY	201 (212)	199 (220)	14 (6.6) [3.9, 10.6]	2 (0.9) [0.2, 3.2]	7.3 [1.7, 31.6]	Feb 22, 2012 – Oct 23, 2014
Pool {Equal Weighting of above studies}	1209 (1488)	1199 (1518)	90 (6.0) [4.9, 7.5] {6.96}	28 (1.9) [1.3, 2.6] {1.44}	5.1 [2.64, 9.70]*	

Source: iPrEX from {Grant et al 2010}; Ipergay from {Molina et al 2015}; PROUD from {McCormack et al 2015}
*Based on equal weighting where all studies are given the same weight.
Pooling where each subject is given the same weight.

Source: Statistical analysis plan GS-US-412-2055

DISCOVER Results

- 5,399 MSM/TGW subjects were randomized
  - Safety Population: 5,387 (F/TAF 2,694; F/TDF 2,693)
  - Full Analysis Set (FAS) Population: 5,335 (F/TAF 2,670; F/TDF 2,665)
- Demographics (Safety Population)
  - Median age: 34 years
  - MSM 99%, TGW 1%
  - White 84%, black/mixed black 9%, Hispanic 25%
  - Truvada PrEP use at baseline 16%
  - Uncircumcised 44%
- Median duration of exposure: 86.1 weeks (Q1,Q3: 83.9, 96.7)
- Adherence to study drug was high by multiple measures

DISCOVER Efficacy

Primary efficacy analysis performed on FAS population

		F/TAF (N=2670)	F/TDF (N=2665)	Ratio of F/TAF vs. F/TDF (95.003% CI)
Person-years of Follow-Up		4369.7	4386.2	
Number of HIV-1 Infected Events		7	15	
HIV-1 Infection Rate per 100 Person-years		**0.160**	**0.342**	
Sponsor used	95% Exact CI[a]	(0.064, 0.330)	(0.191, 0.564)	
	Rate Ratio	**0.468**		(0.191, **1.149**)[b]

a: Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
b: 95.003% CI was constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect.

Source: FDA statistical analysis

90-day update: one additional HIV infection reported in F/TAF group – does not impact primary efficacy conclusion

Efficacy Against Penile HIV-1 Exposures

- Direct evidence to support efficacy of F/TAF for this low-risk route of transmission is lacking
- In DISCOVER trial, insertive sex was occurring:
  - Subjects reported a mean of 4 unprotected insertive anal intercourse (UIAI) partners in the 90 days prior to screening
  - During trial, 16% of subjects had urethritis diagnosed with gonorrhea or chlamydia (likely from UIAI)
- Given the low rates of HIV-1 infection observed in DISCOVER, it may be reasonable to assume that men who practice insertive sex were protected

DISCOVER Safety

- Both F/TAF and F/TDF were safe and well tolerated
- No notable differences observed between arms in types, incidence, severity, or onset of adverse events (AEs) or laboratory abnormalities
- Most common AEs were sexually-transmitted infections (STIs)
  - Most common non-infectious AEs: diarrhea (16%), nausea (7%), headache (7%), and fatigue (6%), with comparable rates between arms

DISCOVER Safety

- Serious AEs: F/TAF 6% vs. F/TDF 5%
  - Majority not considered related to study drug
- Low rates of AEs leading to drug discontinuation: F/TAF 1% vs. F/TDF 2%
  - Most common AEs leading to drug discontinuation: gastrointestinal disorders (F/TAF 0.3% vs. F/TDF 0.6%)
- GI events tended to occur in first month of treatment
- Mean (SD) change from baseline in weight at Week 48:
  - F/TAF +1.1 (4.3) kg vs. F/TDF -0.1 (4.4) kg

DISCOVER Safety – Renal

Mean (SD) Change in SCr (mg/dL)

Week 48:

F/TAF: -0.01 (0.11)

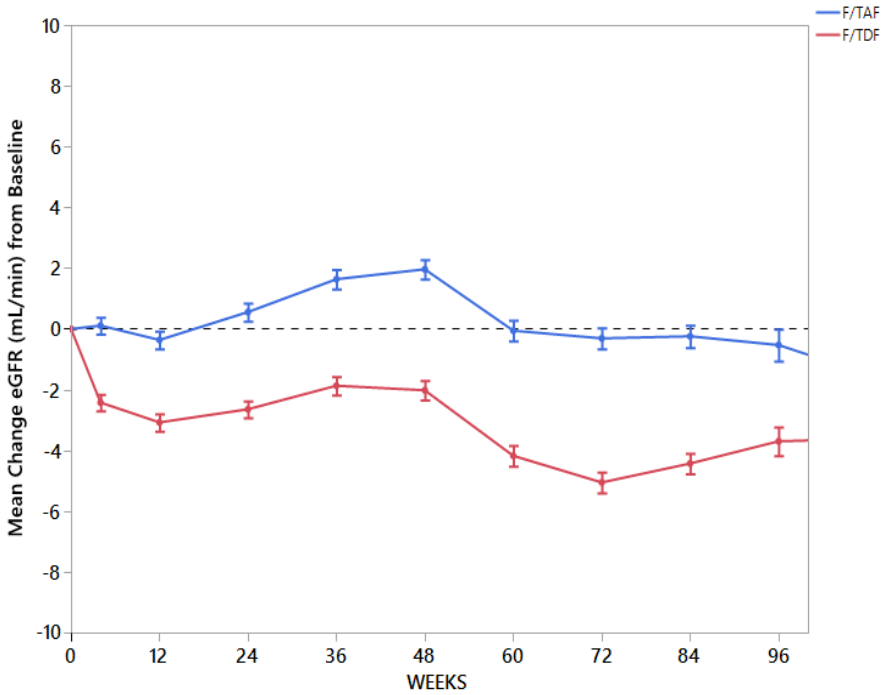
F/TDF: +0.01 (0.11)

Week 96:

F/TAF: +0.01 (0.12)

F/TDF: +0.02 (0.12)

Mean Change in $eGFR_{CG}$ (mL/min)



Source: FDA analysis

SCr = serum creatinine; $eGFR_{CG}$ = estimated glomerular filtration rate by Cockcroft-Gault method

DISCOVER Safety – Renal

Proteinuria by Quantitative Assessment

Urine Protein/Creatinine Ratio (UPCR)

	F/TAF		F/TDF	
	Baseline		Baseline	
	≤200 mg/g (N=2662)	>200 mg/g (N=25)	≤200 mg/g (N=2657)	>200 mg/g (N=25)
Week 48				
≤200 mg/g	2318 (99%)	12 (57%)	2296 (98%)	8 (44%)
>200 mg/g	17 (1%)	9 (43%)	35 (2%)	10 (56%)

Denominator for percentages = number of subjects with nonmissing values at baseline and postbaseline visit

DISCOVER Safety – Renal

Treatment-emergent Proteinuria by Urine Dipstick

	F/TAF	F/TDF
Urine Protein	N=2671	N=2662
Any Grade	568 (21%)	647 (24%)
Grade 1	518 (19%)	592 (22%)
Grade 2	50 (2%)	55 (2%)

DISCOVER Safety – Renal

Graded Treatment-emergent Laboratory Abnormalities

	F/TAF	F/TDF
Creatinine (mg/dL)	N=2672	N=2665
Any Grade	28 (1%)	64 (2%)
Grade 1	23 (1%)	61 (2%)
Grade 2	5 (0.2%)	3 (0.1%)
Hypophosphatemia (mg/dL)	N=2672	N=2665
Any Grade	237 (9%)	226 (9%)
Grade 1	144 (5%)	143 (5%)
Grade 2	87 (3%)	76 (3%)
Grade 3	6 (0.2%)	5 (0.2%)
Grade 4	0	2 (<0.1%)

DISCOVER Safety – Renal

Renal Adverse Events

MedDRA High Level Term	MedDRA Preferred Term	F/TAF N=2694	F/TDF N=2693
Glomerulonephritis/nephrotic syndrome	Nephrotic Syndrome	1 (<0.1%)	0
Nephropathies and tubular disorders		1 (<0.1%)	1 (<0.1%)
	Fanconi syndrome acquired	0	1 (<0.1%)
	Glomerulonephropathy	1 (<0.1%)	0
Renal failure and impairment		13 (1%)	19 (1%)
Urinary abnormalities		64 (2%)	65 (2%)
Mineral and electrolyte analyses	Blood phosphorus decreased	3 (0.1%)	1 (<0.1%)
Renal function analyses		15 (1%)	34 (1%)
Urinalysis NEC		8 (0.3%)	7 (0.3%)

DISCOVER Safety – Renal

Renal Adverse Events Leading to Drug Discontinuation

	F/TAF N=2694	F/TDF N=2693
Any AE Leading to Drug Discontinuation	5 (0.2%)	8 (0.3%)
Acute kidney injury	2 (0.1%)	2 (0.1%)
Fanconi syndrome acquired	0	1 (<0.1%)
Proteinuria	0	1 (<0.1%)
Renal impairment	0	2 (0.1%)
Blood creatinine increased	3 (0.1%)	1 (<0.1%)
Glomerular filtration rate decreased	0	1 (<0.1%)

DISCOVER Safety – Bone

Bone Mineral Density (BMD) DXA substudy (F/TAF 200; F/TDF 198)

	Visit	Mean (SD) % Change from Baseline	
		F/TAF	F/TDF
Hip	Week 48	N= 158 **+0.18% (2.4)**	N=158 **-0.99% (2.4)**
	Week 96	N=100 **+0.42% (2.6)**	N=105 **-1.2% (2.9)**
Spine	Week 48	N=159 **+0.5% (3)**	N=160 **-1.12% (3)**
	Week 96	N=100 **+0.88% (3.1)**	N=112 **-1.25% (3.9)**

DXA =dual-energy X-ray absorptiometry

DISCOVER Safety – Bone

Categorical Analysis: % Change in BMD from Baseline

	Week 48	F/TAF N=190	F/TDF N=188
Hip	≥ 7% decrease from baseline	2/158 (1%)	2/158 (1%)
	≥ 7% increase from baseline	1/158 (1%)	1/158 (1%)
Spine	≥ 5% decrease from baseline	7/159 (4%)	7/160 (4%)
	≥ 5% increase from baseline	9/159 (6%)	3/160 (2%)

DISCOVER Safety – Bone

Categorical Analysis: Change in BMD Clinical Status from Baseline to Week 48 - Spine

Baseline Spine Clinical Status

T-score	Clinical Status	F/TAF N=190	F/TDF N=188
≥-1	Normal	138	134
<-1 to ≥2.5	Osteopenia	46	50
<-2.5	Osteoporosis	6	4

Worsened Status

F/TAF: 2/154 (1%)
F/TDF: 10/156 (6%)

Improved Status

F/TAF: 8/40 (20%)
F/TDF: 4/47 (9%)

DISCOVER Safety – Bone

Categorical Analysis: Change in BMD Clinical Status from Baseline to Week 48 - Hip

Baseline Hip Clinical Status

T-score	Clinical Status	F/TAF N=190	F/TDF N=185
≥-1	Normal	146	138
<-1 to ≥2.5	Osteopenia	43	47
<-2.5	Osteoporosis	1	0

Worsened Status

F/TAF: 5/157 (3%)
F/TDF: 5/158 (3%)

Improved Status

F/TAF: 3/38 (8%)
F/TDF: 5/40 (13%)

DISCOVER Safety – Bone

	F/TAF N=2694	F/TDF N=2693
All fractures	53 (2%)	53 (2%)
Pathological fractures	1 (<0.1%)	2 (<0.1%)
Back pain	98 (4%)	103 (4%)
Spinal pain	4 (0.2%)	8 (0.3%)
Bone pain	2 (<0.1%)	3 (0.1%)
Bone density decreased	5 (0.2%)	1 (<0.1%)
Bone loss	1 (<0.1%)	1 (<0.1%)
Osteopenia	12 (0.5%)	15 (0.6%)
Osteoporosis	5 (0.2%)	7 (0.3%)
Blood phosphorus decreased	3 (0.1%)	1 (<0.1%)

DISCOVER Safety – Lipids

Median Change from Baseline in Fasting Lipids

Lipid Parameter	Visit	F/TAF	F/TDF
Total Cholesterol (mg/dL)	Week 48	-1	-11
	Week 96	-4	-14
LDL (low density lipoprotein) (mg/dL)	Week 48	+1	-6.5
	Week 96	-4	-8
Total Cholesterol:HDL (high density lipoprotein) Ratio	Week 48	+0.11	+0.12
	Week 96	+0.03	-0.01
Triglycerides (mg/dL)	Week 48	+4	0
	Week 96	+2	-5

DISCOVER Safety – Lipids

Graded Treatment-emergent Lipid Abnormalities

	F/TAF	F/TDF
Total cholesterol (mg/dL)	N=2371	N=2380
Any Grade	900 (38%)	570 (24%)
Grade 1	689 (29%)	466 (20%)
Grade 2	191 (8%)	100 (4%)
Grade 3	20 (1%)	4 (<1%)
LDL (mg/dL)	N=2362	N=2377
Any Grade	705 (30%)	482 (20%)
Grade 1	513 (22%)	376 (16%)
Grade 2	141 (6%)	88 (4%)
Grade 3	51 (2%)	18 (1%)
Triglycerides (mg/dL)	N=2371	N=2380
Any Grade	39 (2%)	21 (1%)

DISCOVER Safety – Lipids

Categorical Analysis: Change in NCEP LDL Category from Baseline to Week 48

Baseline LDL Category

LDL	F/TAF N=2694	F/TDF N=2693
<100	720	721
100-159	629	656
160-190	52	50
>190	11	17

Worsened LDL Category

F/TAF: 188/1139 (17%)
F/TDF: 114/1156 (10%)

Improved LDL Category

F/TAF: 157/572 (28%)
F/TDF: 234/587 (40%)

NCEP = National Cholesterol Education Program

DISCOVER Safety – Summary

- F/TAF and F/TDF were both safe and well tolerated
- Differences between groups were noted in various indices, i.e., change from baseline in renal biomarkers, BMD on DXA scans, and fasting serum lipids, consistent with previous trials that compare TAF to TDF
- In general, F/TAF and F/TDF had similar adverse event profiles
- Low rates of serious AEs or AEs leading to drug discontinuation with both drugs

DESCOVY® for PrEP in Cisgender Women

Considerations for Conducting a PrEP Trial in Cisgender Women

- Previous clinical trials in cisgender women have demonstrated variable efficacy of oral F/TDF, mostly driven by adherence

- FDA recommends superiority designs for trials in cisgender women because determination of a non-inferiority margin is not readily feasible in this population

Extrapolation of Efficacy to Cisgender Women: Approaches Proposed by the Applicant

1) F/TAF to F/TAF

Extrapolation of F/TAF efficacy from MSM to cisgender women

- Demonstrate comparable *systemic exposures* between men and cisgender women
  - TFV and TAF concentrations in plasma
  - TFV-DP concentrations in PBMCs

2) F/TDF to F/TAF

Extrapolation of F/TDF efficacy

- Makes use of published EC90 value (40 fmol/million cells in PBMCs) from iPrEx trial of F/TDF in MSM
- Demonstrate comparable or higher TFV-DP concentrations in systemic and cervicovaginal tissue with TAF relative to TDF

Approach 1: F/TAF in MSM → F/TAF in Cisgender Women

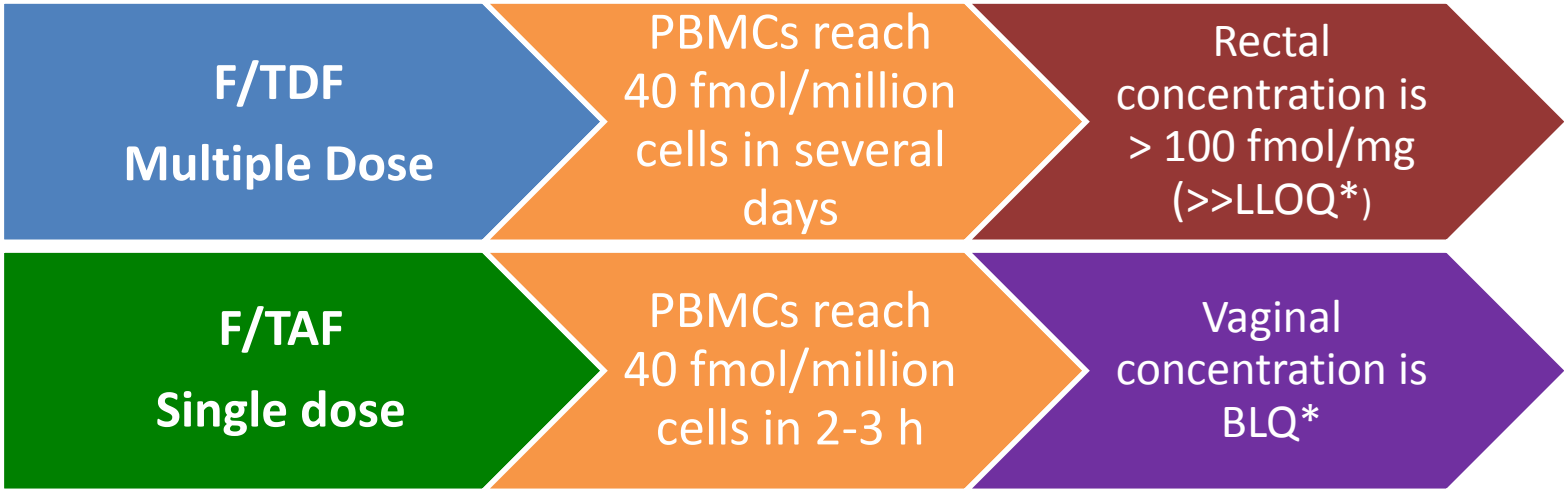
- There is no expected clinically relevant difference in the PK of FTC, TAF or PBMC-associated TFV-DP between men and women
- However, matching systemic drug exposures alone may not suffice because of the unknown contribution of mucosal tissue concentrations to PrEP efficacy

Approach 2.1: F/TDF → F/TAF

- Applicant has cited 40 fmol of TFV-DP per million cells in PBMCs as “threshold” or “EC90 value” for PrEP efficacy
  - Concentration is associated with adherence to ~3-4 doses per week in MSM from the iPrEx trial
  - Concentration has not been validated as a PK surrogate for tenofovir-based PrEP efficacy for all populations

Approach 2.1: F/TDF → F/TAF

- 40 fmol/million cells in PBMCs may correlate to different TFV-DP concentrations in relevant mucosal tissues



*LLOQ= lower limit of quantification; BLQ= below limit of quantification

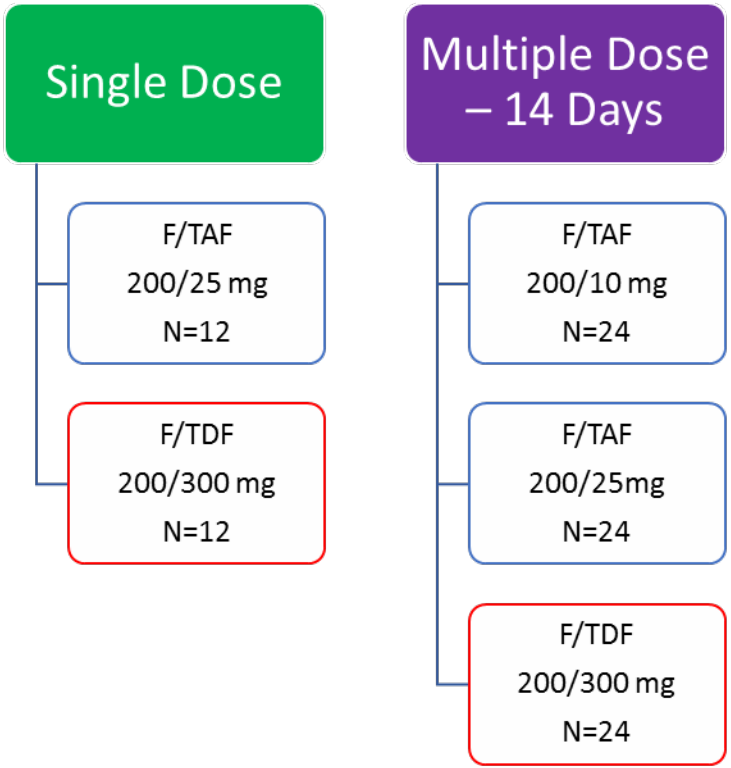
Louissaint N, et al. AIDS Res Hum Retroviruses 2013; 29:1443-50; Cottrell M, et al. J Antimicrob Chemother 2017; 72: 1731-40; Seiffert S, et al. AIDS Res Hum Retroviruses 2016; 32:981-91; Hendrix C, et al. AIDS Res Hum Retroviruses 2016; 32:32-43

Approach 2.2: F/TDF in cisgender women → F/TAF in cisgender women

- Efficacy may be extrapolated from F/TDF to F/TAF if **both** systemic and mucosal tissue TFV-DP exposures are higher with F/TAF than F/TDF in cisgender women

Systemic	• TAF has higher levels of TFV-DP in PBMCs 
Tissue Cervical and Vaginal	• Single-dose TAF or TDF results in mostly BLQ • Multiple-dose TAF or TDF → Study A15-137 

Study A15-137: Study Design



PK Samples

- Multiple samples collected
  - plasma, PBMC, rectal and cervicovaginal fluid, tissue biopsies
- Focus on rectal, cervical and vaginal tissue biopsies
  - Evaluated for **TFV-DP**, TAF, TFV, FTC, FTC-TP, dATP and dCTP
  - Each subject contributed cervicovaginal tissue samples at only one given timepoint

Study A15-137: Tissue Sample Collection

- Tissue samples were collected at different clinical sites at different time points
  - Rectal tissues: 4 hours post dose following 14-day administration
  - Cervical and vaginal tissues:
    - 4 hours post-dose following single dose administration
    - 4, 24, and 48 hours following 14-day administration
- Measurement: Tissue homogenates
- Assuming a tissue density of 1 g/mL, final sample concentrations and the lower limit of quantitation (LLOQ of 0.3 ng/mL) were converted to fmol/g for TFV-DP

Study A15-137: Results

- Following **single dose** administration of F/TAF or F/TDF, 83% of vaginal tissue samples were below the lower limit of quantitation (BLQ) at 4 hours
- Following **multiple doses** of F/TAF or F/TDF, a significant proportion of tissue PK samples were BLQ
  - In vaginal tissues, TFV-DP concentrations were higher for F/TAF compared to F/TDF only at 4 hours post-dose, but were mostly unquantifiable at 24 and 48 hours
  - Unclear if this translates to comparable or higher TFV-DP concentrations beyond 4 hours after multiple dose administration

Study A15-137: Multiple Dose Results

		Vaginal tissue		Cervical tissue		Rectal tissue	
		F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
4 hours	% BLQ*	0% (0/8)	62% (5/8)	25% (2/8)	88% (7/8)	31% (9/29)	3% (1/30)
	Median TFV-DP† (fmol/mg)	151	N/A	126	N/A	150	2,521
24 hours	% BLQ*	80% (12/15)	69% (11/16)	67% (10/15)	81% (13/16)	Not Collected	
	Median TFV-DP† (fmol/mg)	N/A	N/A	N/A	N/A		
48 hours	% BLQ*	80% (12/15)	79% (11/14)	93% (14/15)	100% (14/14)		
	Median TFV-DP† (fmol/mg)	N/A	N/A	N/A	N/A		

* Percentage of samples below the lower limit of quantitation (BLQ) = number of samples BLQ/ total number of samples
† Median values of all subjects, including those with a value of BLQ; concentrations BLQ were imputed as 0.5 * LLOQ
N/A = cannot be determined as the median concentration value was BLQ

Conclusions

- F/TAF and F/TDF afford similar protection against sexual acquisition of HIV-1 infection in MSM/TGW at substantial risk
- Both F/TAF and F/TDF are safe and well tolerated
  - F/TAF results in smaller changes or improvements from baseline in biomarkers of proteinuria and bone mineral density compared to F/TDF, but less favorable lipid changes
  - No major differences noted with respect to side effect profile

Conclusions

- Clinical data regarding use of F/TAF for PrEP in cisgender women are lacking
- Robust TFV-DP concentration data in the female genital tract are lacking
- Application proposes a PrEP indication in cisgender women based on extrapolation of efficacy data via TFV-DP concentrations in peripheral blood mononuclear cells
- However, the relative importance of mucosal tissue vs. systemic drug concentrations to PrEP efficacy is unknown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BACK UP SLIDES SHOWN

TGW: potential drug interactions between TAF and feminizing regimens?

- Commonly used feminizing regimens in TGW
  - Estrogens (estradiol and conjugated estrogens) and androgen blockers (e.g., cyproterone, spironolactone, leuprolide)
- No clinical drug interaction study has been conducted with TAF and feminizing regimens
  - CYP-based drug interactions are likely to be minimal
  - However, some studies suggest that estrogen can change phosphorylation/dephosphorylation of nucleosides and their analogues
- Studies conducted with TDF in TGW receiving feminizing regimens
  - Minimal changes in plasma TFV concentrations
  - Minimal changes in TFV-DP concentrations in PBMC or rectal tissue
  - Similar dATP to cisgender men but significantly higher dATP (> 20-fold) in rectal tissues (but not in PBMC)
    - May lower effective concentrations of TFV-DP in rectal tissues

Cottrell 2019 CID, Hiransuthikul JIAS 2019, Hendrix HIV4RP2018

TFV-DP concentrations in rectal and vaginal mononuclear cells

- At this time, little is known regarding TFV-DP concentrations in rectal or vaginal mononuclear or CD4+ cells following the administration of TDF or TAF. Therefore, it is unknown whether TFV-DP concentrations in rectal or vaginal mononuclear cells are more closely correlated to PBMC or mucosal tissue homogenates .
- Two published studies with TDF have shown conflicting results, and interpretation is limited by the small number of subjects/samples and differences in study design
  - Seifert 2016: Significantly higher (> 10-fold) TFV-DP concentrations in rectal mononuclear cells as compared to PBMC.
  - Louissaint 2013: Similar TFV-DP concentrations between blood CD4+ cells and rectal CD4+ cells at C_{24}, but 14-fold higher TFV-DP concentrations in rectal tissue homogenates as compared to PBMC.

Comparison of Lower Limit of Quantitation Across Publications

- General steps taken for TFV-DP quantitation in mucosal tissues: homogenization → protein precipitation extraction → (additional steps may be taken for further isolation of TFV-DP)→ Liquid chromatography-Mass spectrometry (LC/MS)
- Various methods/conditions have been used for homogenization, protein precipitation, and chromatographic methods, which may have resulted in differences in assay sensitivity. In addition, some studies are not as rigorously validated as others.
- Published studies used incompatible units for the lower limit of quantitation (e.g., fmol/sample or ng/mL), which makes it difficult to compare assay sensitivities across studies

	A15-137	Cottrell 2017	Hendrix 2016
LLOQ values reported as fmol/mg tissue (median values)	Rectal:~90 fmol/mg FGT: ~50 fmol/mg	Rectal: 1 fmol/mg FGT: 6 fmol/mg	Rectal: 5 fmol/mg FGT: 5 fmol/mg

FGT: female genital tract

- The difference in LLOQ can be due to: 1) tissue biopsy size 2) sample storage stability, 3) sample recovery efficiency and 4) assay sensitivity

A15-137 bioanalytical report, Cottrell 2017 JAC, Hendrix 2016 ARHR