Descovy for PrEP in Women

James F Rooney MD
Gilead Sciences

MTN Regional Meeting
Sept 2019

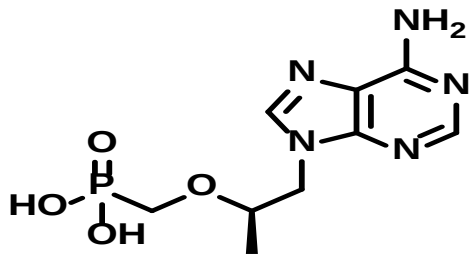
Agenda

- What is TAF and what is Descovy (TAF/FTC)?
- How is Descovy different than Truvada?
- The Discover Trial in MSM/transgender women
- Descovy PrEP for women
  - Monkey vaginal challenge studies
  - Phase 1 PK data in women
  - Safety data for HIV treatment in women
- FDA Advisory Committee August 2019
- Future studies of Descovy for PrEP in women

TDF and TAF: Two Prodrugs to Deliver Tenofovir

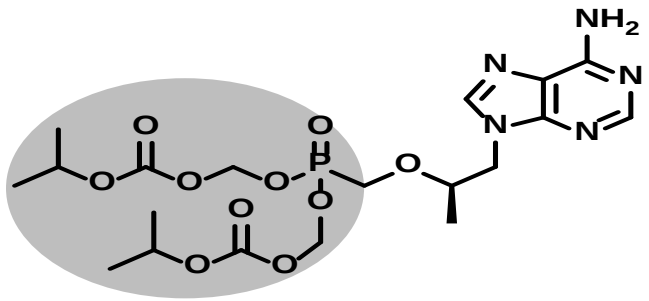
Tenofovir
(TFV)

Dianion



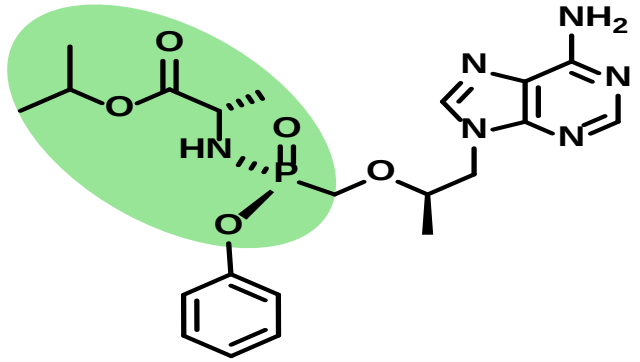
Tenofovir disoproxil
fumarate (TDF)
(Prodrug)

Ester



Tenofovir alafenamide
(TAF)
(Prodrug)

Amidate

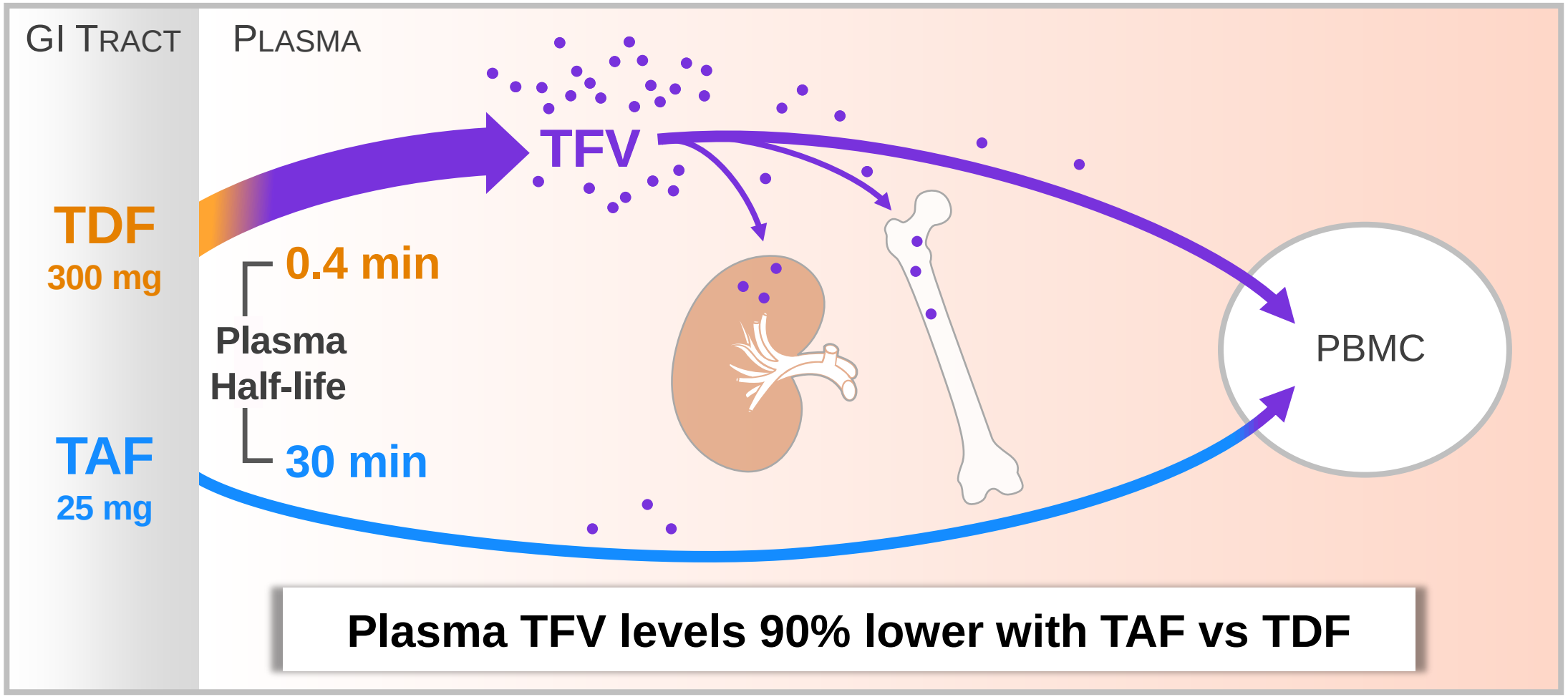


- **TDF (in combination with FTC) is the N(t)RTI combination currently recommended in PrEP guidelines**
- **TDF has some limitations:**
  - Not recommended for HIV-1 PrEP when CrCL < 60 mL/min; renal safety considerations; Loss of bone mineral density[2]
  - Likely relationship between plasma TFV exposure and renal or bone effects[3]
- **TAF is a prodrug of TFV with distinct metabolism that maximizes antiviral potency and clinical safety**
  - TAF provides comparable efficacy to TDF* at one-tenth the dose, resulting in lower TFV concentration and fewer off-target effects[4]

*For HIV treatment; the efficacy of F/TAF for PrEP has not been evaluated by the FDA

1. Adapted from Zack J, et al. IAS 2015.Vancouver, Canada. Poster #TUPEB275 2. TRUVADA Prescribing information. Gilead Sciences. 2018 3. Van Rompay KK, et al. AAC. 2008;52:3144-60
4. Lee WA, et al. Antimicrob Agents Chemother 2005;49:1898-906

Tenofovir Alafenamide: Longer Half-Life Allows for Lower Dose



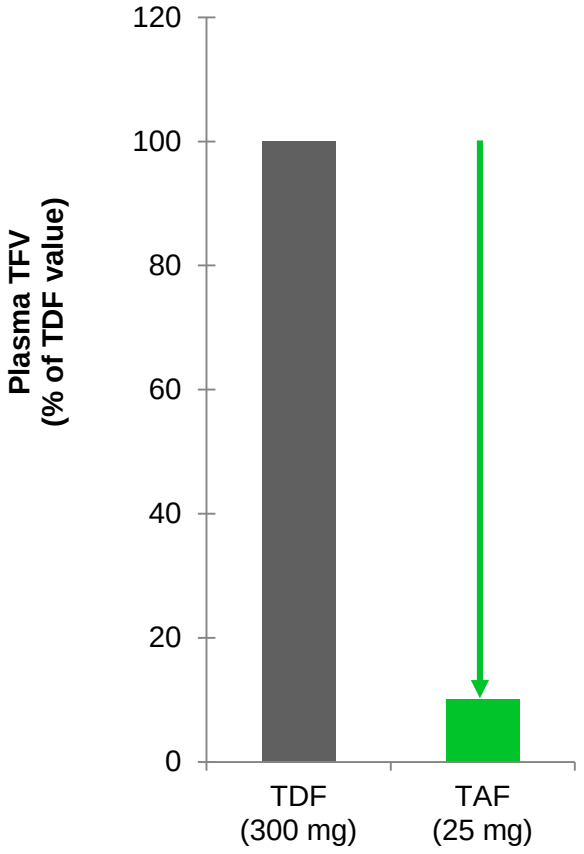
GI=gastrointestinal; PBMC=peripheral blood mononuclear cell; TFV=tenofovir.

Lee W, et al. Antimicr Agents Chemo 2005;49:1898-1906; Birkus G, et al. Antimicr Agents Chemo 2007;51:543-50;
Babusis D, et al. Mol Pharm 2013;10:459-66; Ruane P, et al. J Acquir Immune Defic Syndr 2013; Sax P, et al. JAIDS 2014;67:52-8.

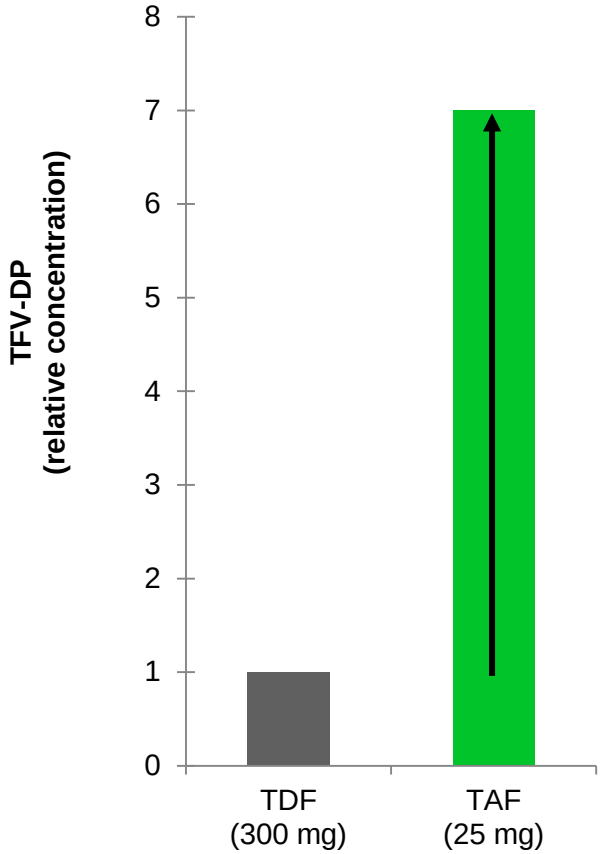
Study GS-US-120-0104

Pharmacokinetic and Virologic Comparison of TAF and TDF

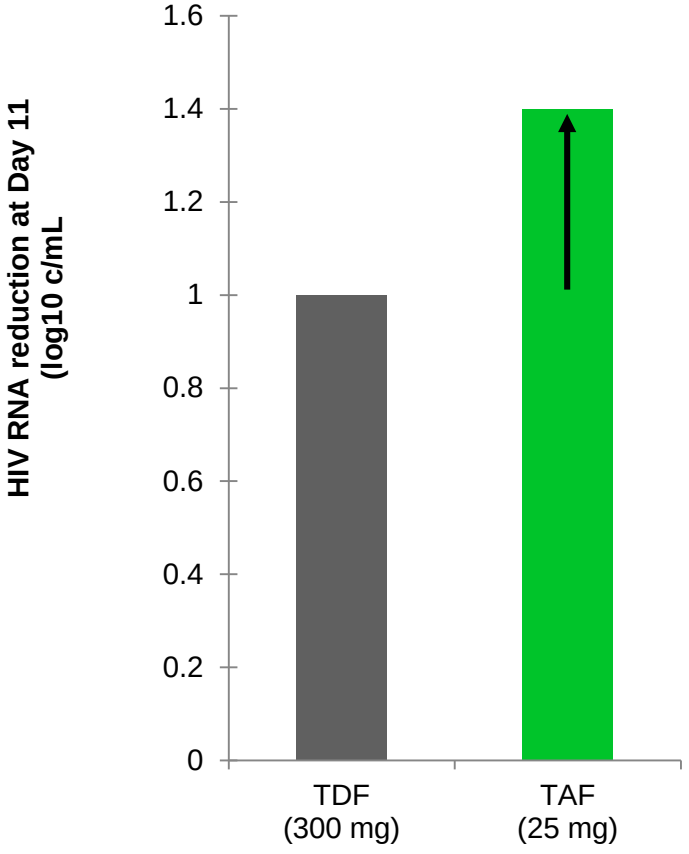
~90% less TFV in plasma



Up to ~7X more TFV-DP in PBMCs



~0.5 Log more in VL reduction

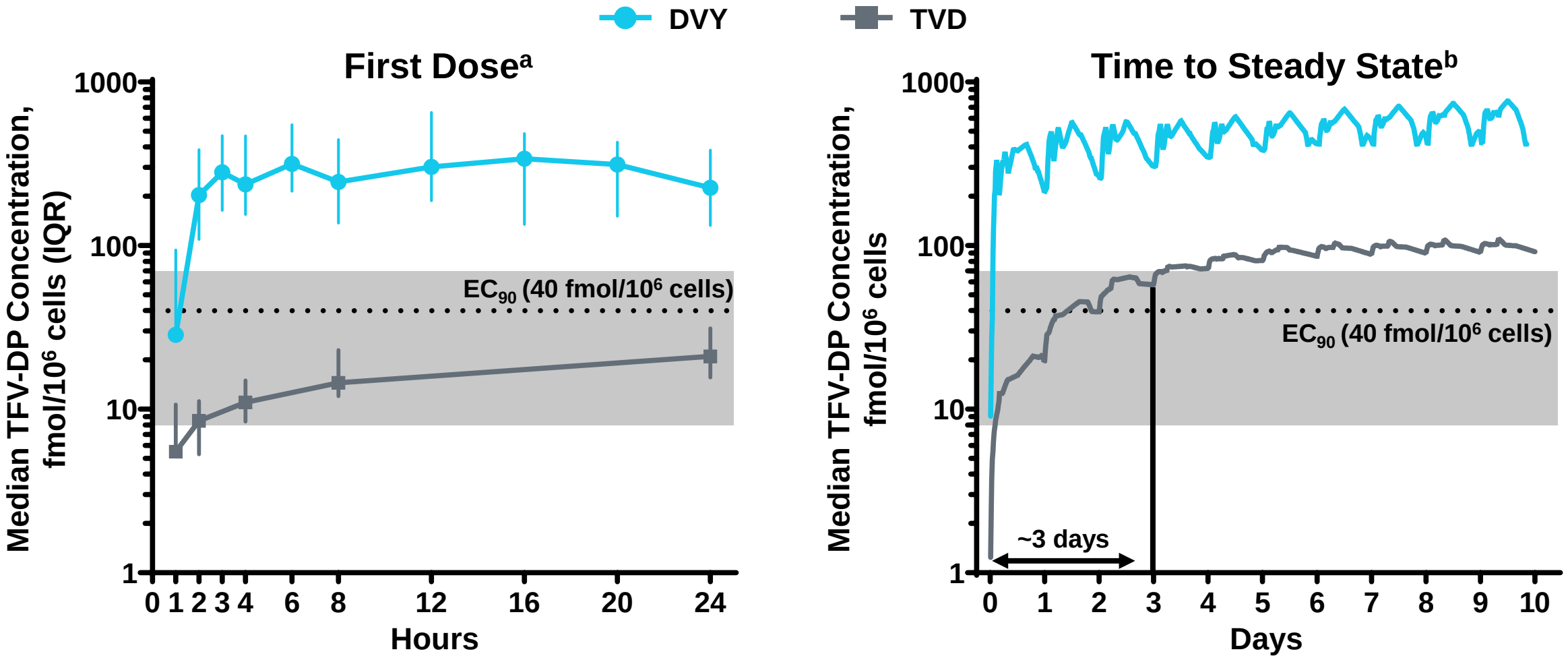


PBMC, peripheral blood mononuclear cell; TFV-DP, tenofovir-diphosphate.

P Ruane, et al. *JAIDS.* 2013; 63:449-445.

Descovy and Truvada TFV-DP Levels in PBMCs

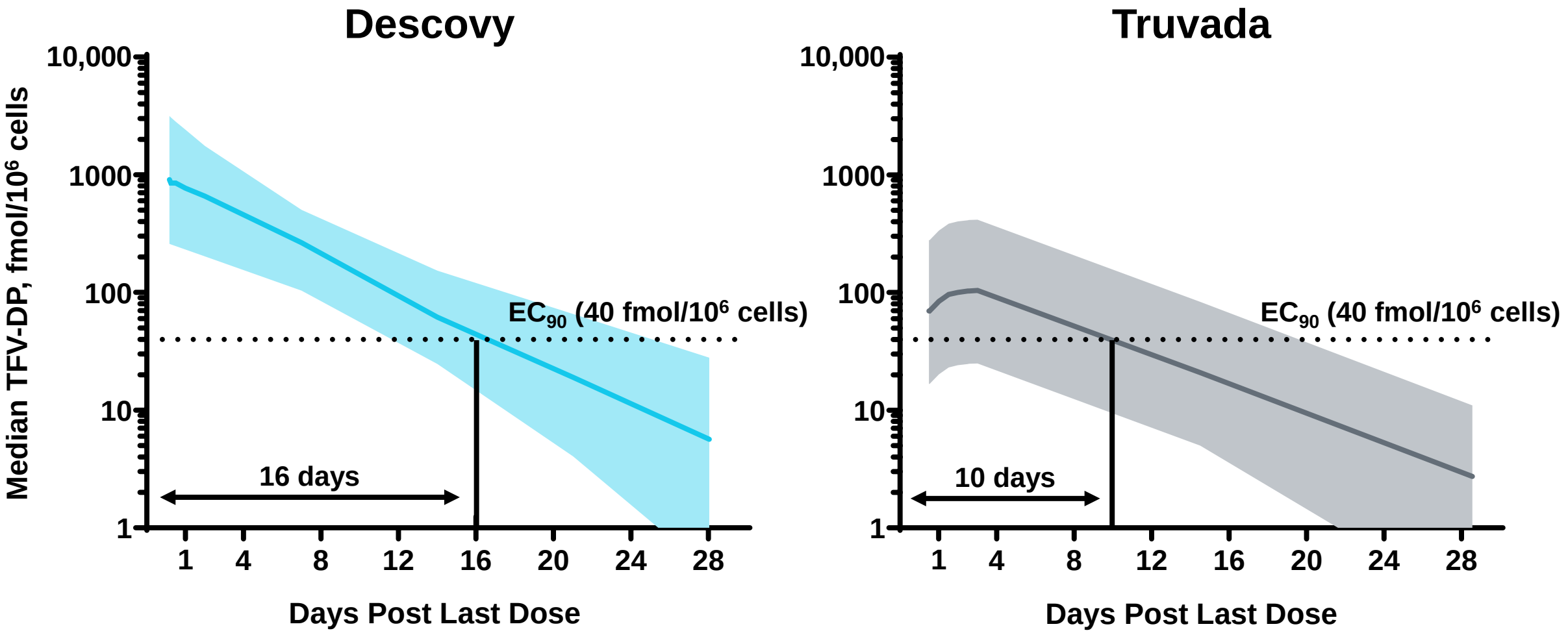
Phase 1 Study in Healthy Volunteers



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



Shading represents 5th–95th percentiles. 1. Anderson PL, et al. CROI 2012; 2. Custodio J, et al. EACS 2017; 3. Custodio J, et al. ASM 2016, poster SUNDAY-410; 4. Hawkins J Acquir Immune Defic Syndr 2005;39:406-11.

‡F/TAF for HIV-1 PrEP is investigational and not been approved by the FDA

Patients May Prefer Smaller Tablet Size

**FTC/TDF*
2012**

~19 mm

**FTC/TAF*
2019‡**

~13 mm

US Dime

~18 mm

*Pills shown are not actual size

Small tablet size may be preferred by patients and has the potential to improve adherence and decrease pill fatigue.[1,2]

1. Data on file. Gilead Sciences. 2019
2. Fields, et al. Curr Ther Res Clin Exp. 2015 Dec; 77: 79–82.

TAF vs TDF summary

- Compared to TDF, TAF has
  - More rapid onset of action
  - Longer duration above EC 90 after discontinuation
  - Higher concentration of intracellular TFV-DP in target cells
  - Lower circulating levels of TFV
  - Smaller pill size
- Compared to TAF, TDF has
  - Increased weight loss
  - Decrease in lipids
- TDF+FTC= Truvada (TVD)
- TAF+FTC= Descovy

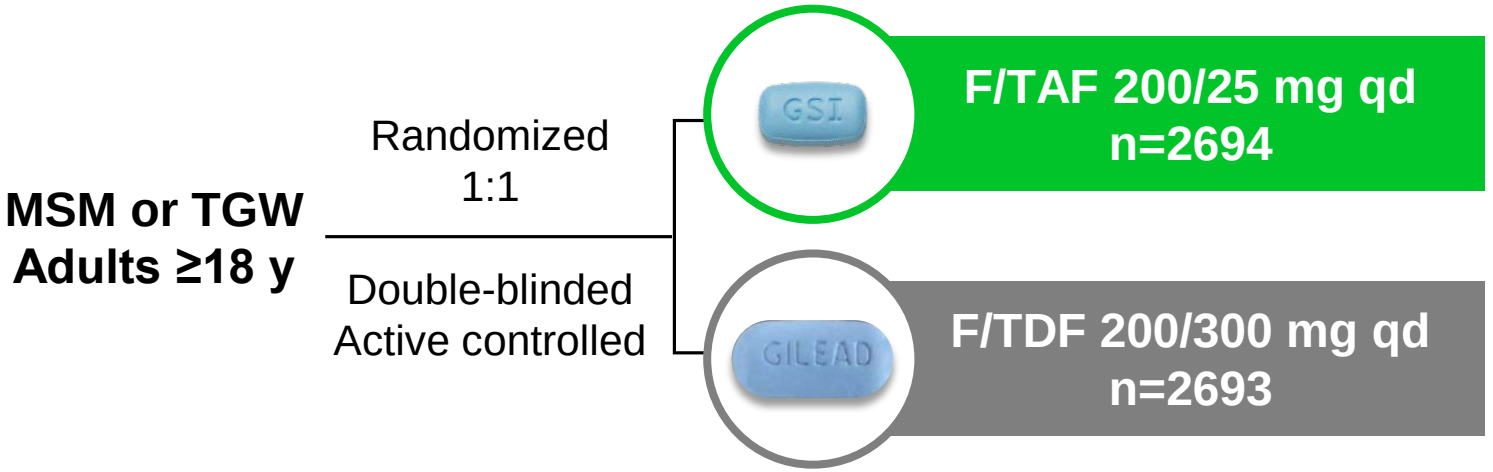
Descovy for Treatment of HIV infection

- TAF/FTC based regimens are the most commonly prescribed treatments for HIV infection in the US, either as Descovy or as part of various single tablet regimens (Biktarvy (bictegravir), Genvoya (boosted elvitegravir), and Odefsy (rilpivirine))
- Descovy is registered in 17 developing world countries and regulatory dossiers have been filed in 17 more
- African countries that have approved Descovy include Nigeria,Tanzania, Zimbabwe, Uganda, Botswana, Madagascar, Ethiopia, Congo, and the Central African Republic
- Voluntary licenses to produce and distribute Descovy have been granted to our generic partners and technology has been transferred
- TAF and FTC were made available to the Medicines Patent Pool for distribution in 116 countries

The DISCOVER Study

Study Design

Randomized, double blind, non-inferiority trial



Primary analysis:

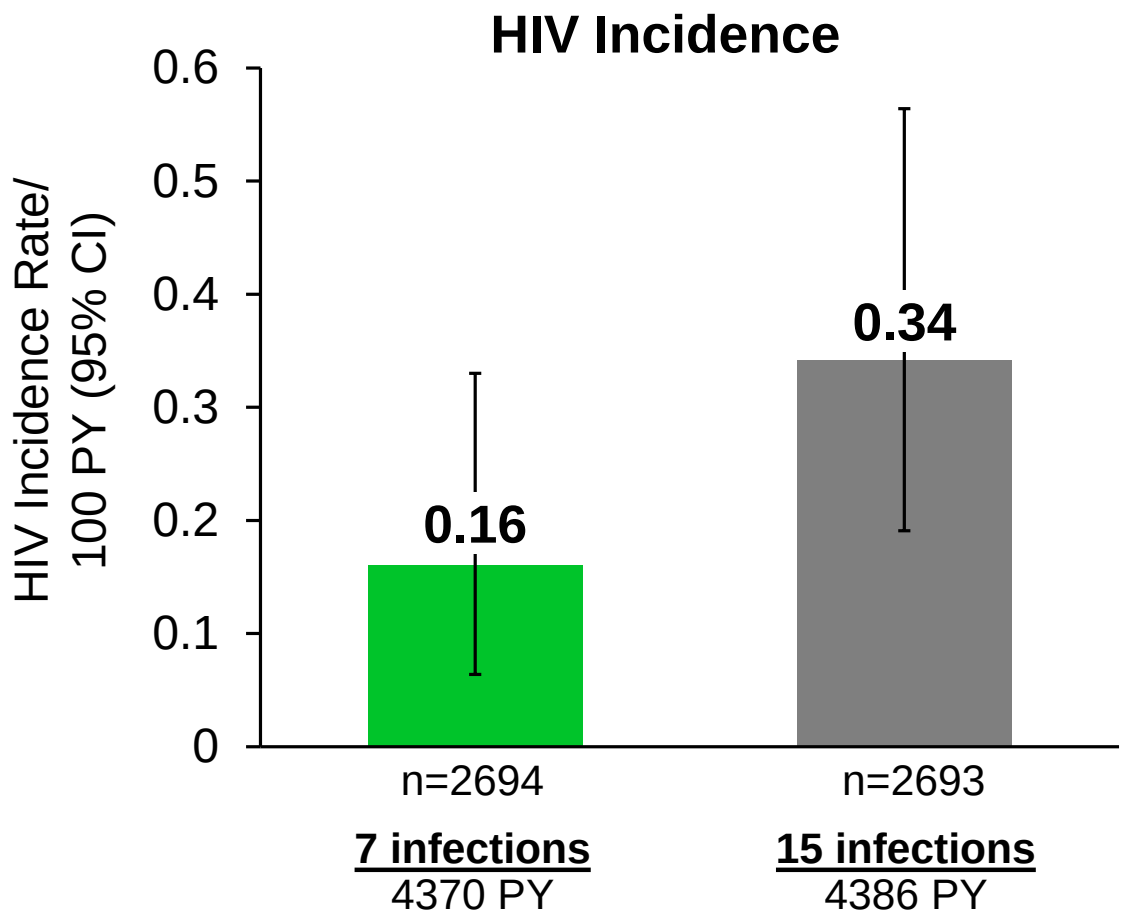
HIV incidence/100 PY when 100% complete Week 48 & 50% complete Week 96

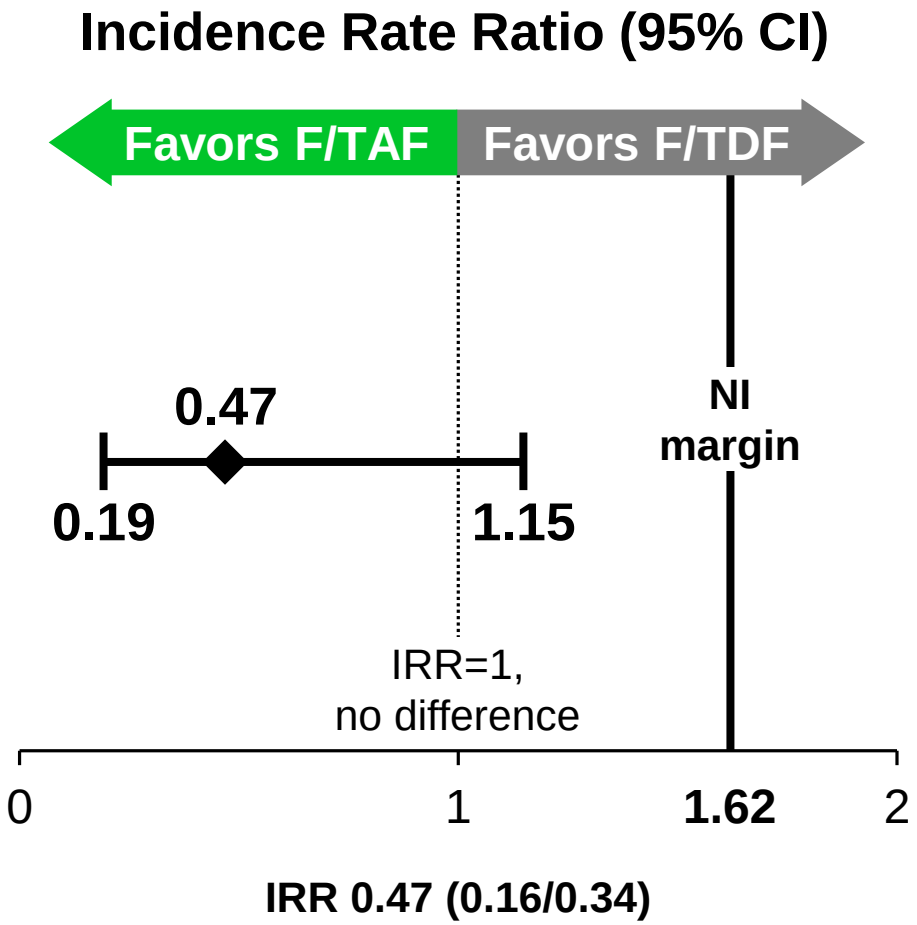
Eligibility criteria

- Sexual behaviors associated with higher risk of HIV acquisition
  - ≥2 episodes of condomless anal sex with ≥2 unique partners in 12 weeks prior to enrollment
  - Diagnosis of rectal gonorrhea, chlamydia, or syphilis in 24 weeks prior to enrollment
- HIV and HBV negative, prior use of PrEP allowed

F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HBV, hepatitis B virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; PY, person-years; TGW, transgender women.

Primary Efficacy Endpoint: Noninferiority Achieved



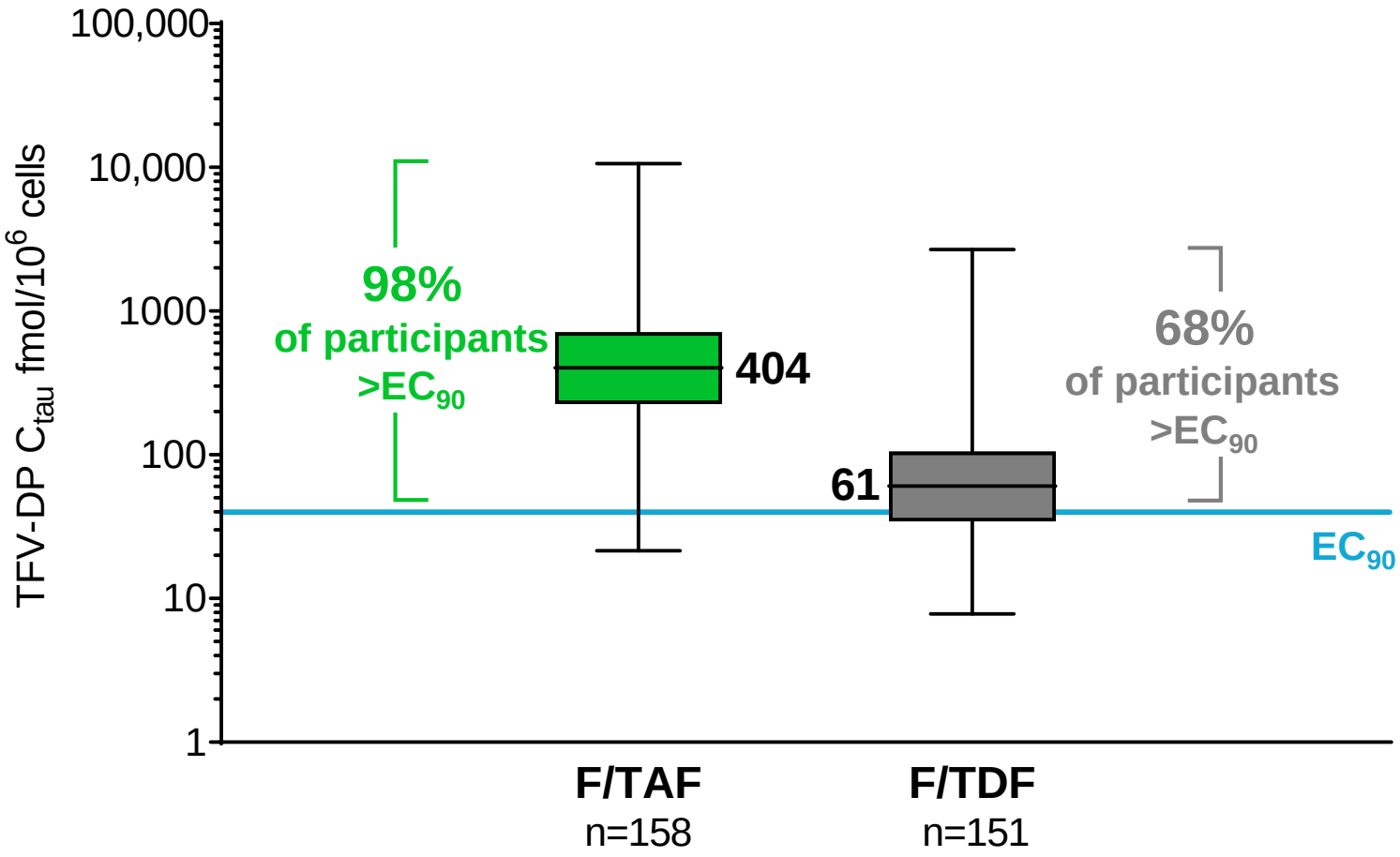


- 22 HIV infections in 8756 PY of follow-up
- Noninferiority was confirmed in sensitivity analysis excluding 5 infections suspected at baseline (1 F/TAF; 4 F/TDF); IRR: 0.55 [0.20, 1.48])

CI, confidence interval; NI, noninferiority
Spinner C. et al. IAS 2019. Mexico City, Mexico. Oral TUAC0403LB

F/TAF Has Higher PBMC TFV-DP Levels vs F/TDF in DISCOVER

Week 4, n=324



- Steady-state TFV-DP levels in PBMCs were 6.3-fold higher with F/TAF vs F/TDF

C_{tau}, concentration 20–28 h postdose. Box median, IQR, whiskers min, max

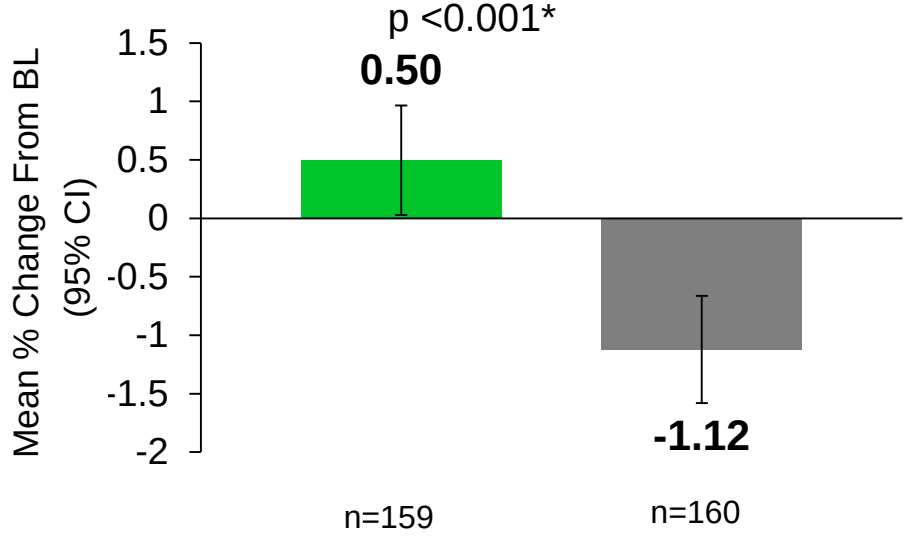
Spinner C. et al. IAS 2019. Mexico City, Mexico. Oral TUAC0403LB

‡

Markers of Bone Safety at Week 48

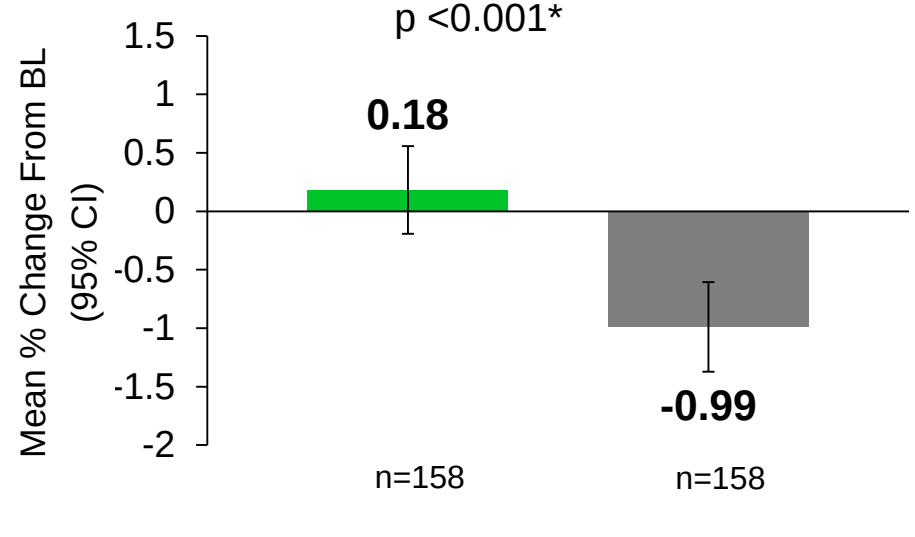
Bone Mineral Density Sub-Study (n=383)

Spine



Change from BL	F/TAF (%)	F/TDF (%)	p-value†
≥3% increase	17	9	0.052
≥3% decrease	10	27	<0.001

Hip



Change from BL	F/TAF (%)	F/TDF (%)	p-value†
≥3% increase	9	6	0.5
≥3% decrease	4	18	<0.001

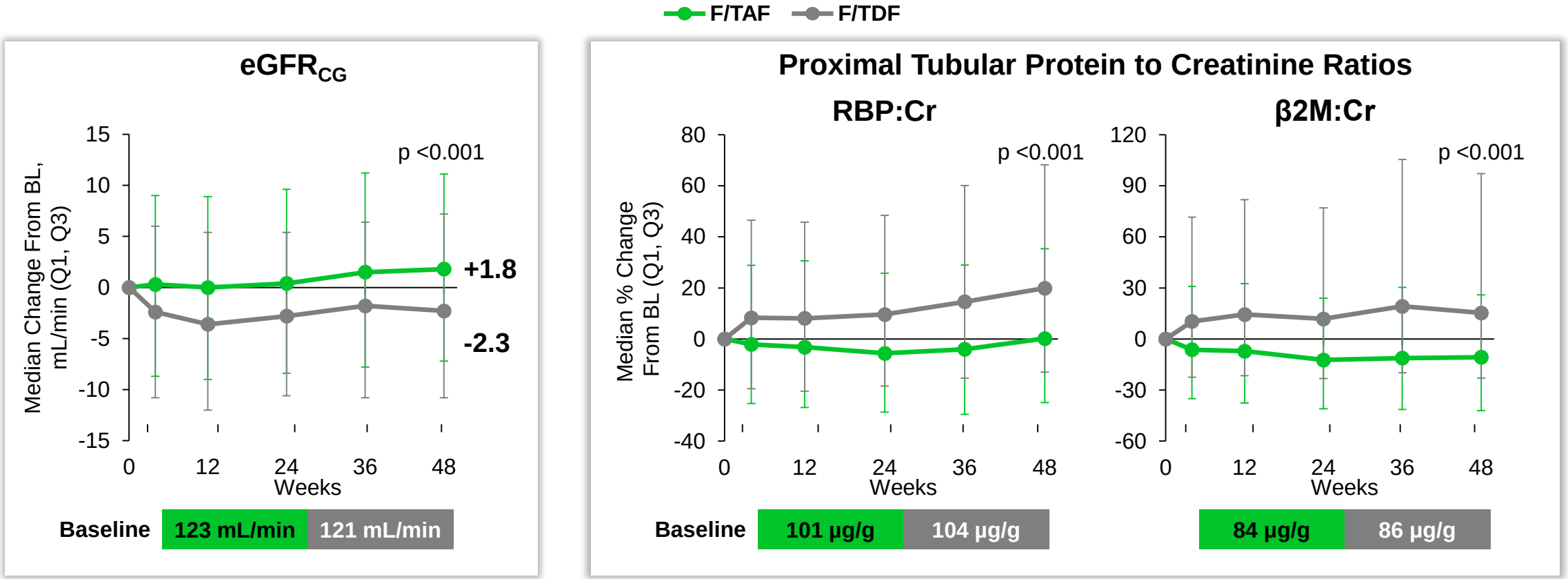
BL, baseline

*p-values from analysis of variance model with baseline F/TDF for PrEP and treatment as fixed effects; †p-value was based on a dichotomized response (ie, ≥3% vs <3%) from Cochran-Mantel-Haenszel test for nominal data (general association statistic) adjusting for baseline F/TDF for PrEP.

Hare B, et al. CROI 2019. Oral 104LB

‡

Markers of Renal Safety Through Week 48



	F/TAF (n)	F/TDF (n)
Renal Discontinuations	2	6
Fanconi Syndrome	0	1

β2M, β2-microglobulin; Cr, creatinine; eGFR$_{CG}$, eGFR by Cockcroft Gault; Q, quartile; RBP, retinol-binding protein.
p-values were from the Van Elteren test stratified by baseline F/TDF for PrEP to compare the 2 treatment groups.

Hare B, et al. CROI 2019. Oral 104LB

Discover Conclusions

- Descovy non-inferior to TVD in HIV incidence
- Low incidence of HIV in both arms with numerically fewer infections in the Descovy arm
- High rate of STDs in this high risk population
- High rates of adherence in both arms with no difference in risk behaviors
- Both drugs were well tolerated with improvements in bone and renal safety markers for Descovy compared with TVD
- Higher levels of TFV-DP in PBMCs in the Descovy arm may have contributed to the fewer number of infections in that group

Descovy PrEP for women

Descovy for PrEP in Women…. Rationale

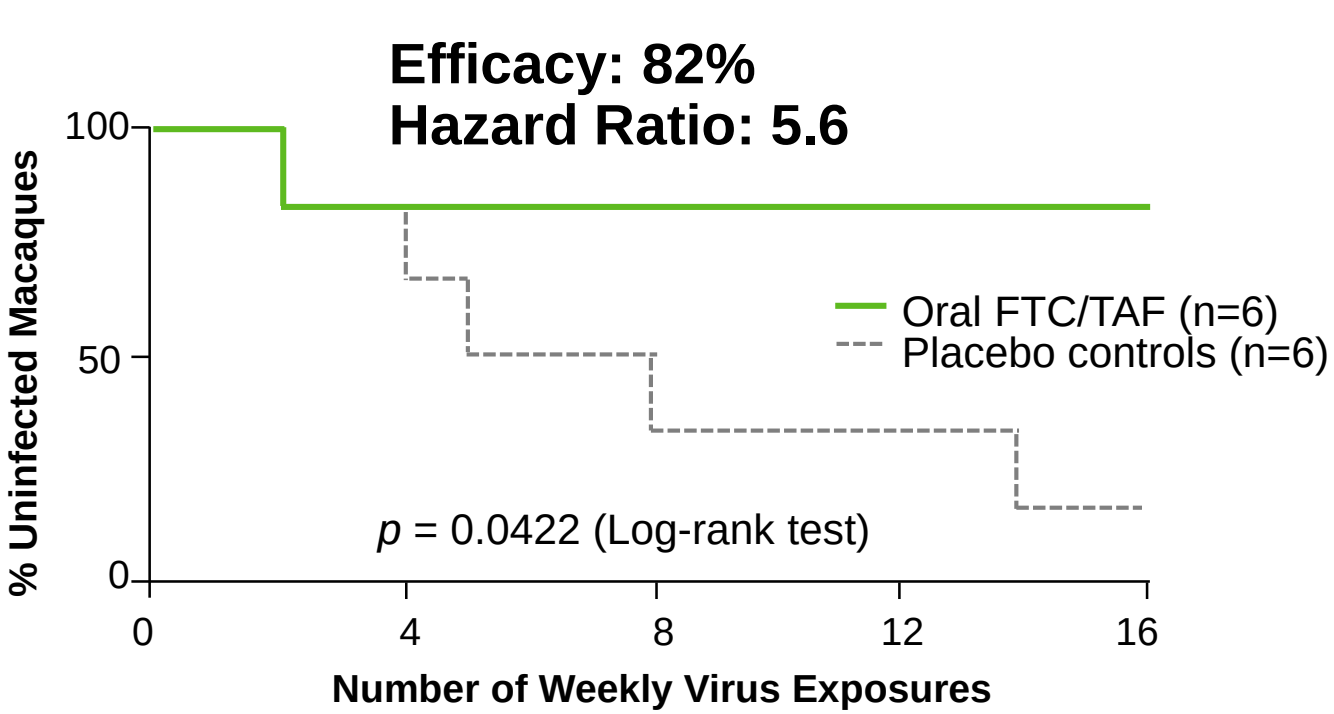
- Descovy approved for treatment of HIV in women and efficacy similar to men
- Improved safety profile of Descovy in HIV infected women compared to Truvada with respect to renal and bone (may be especially important for women who breast feed or take hormonal contraceptives)
- TFV-DP levels in PBMCs 5- 7 fold higher for Descovy vs Truvada
  - Established marker of protection in MSM
- Cervicovaginal tissue levels of TFV-DP similar for Descovy and Truvada (within the limitations of assay sensitivity)
- Descovy as effective as TVD in monkey vaginal challenge models
- Same active inhibitors TFV-DP/FTC-TP for both drugs

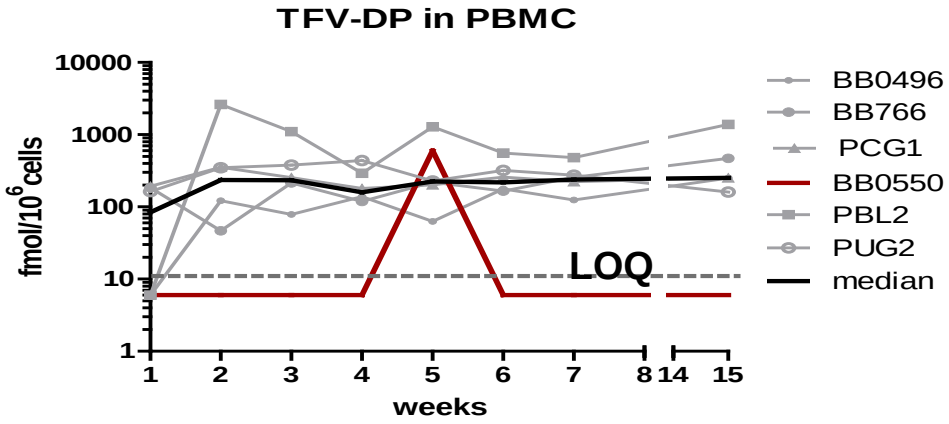
Potential advantages of Descovy vs Truvada for PrEP in the developing world

- Smaller pill
- Cost savings
  - Descovy will be less expensive than Truvada
  - 25 mg dose of TAF vs 300 mg dose of TVD; FTC dose the same 200 mg
- Improved bone and renal safety profile
  - May be especially important for women who are breast feeding or taking hormonal contraceptives
- Gilead access program will make Descovy available for treatment and hopefully prevention
  - Will need a prevention indication

Oral FTC/TAF Prevents Vaginal SHIV Infection in Pigtail Macaques

Vaginal SHIV-challenge study of oral FTC/TAF in HIV-uninfected pigtail macaques (N=12)





- TFV-DP concentrations in PBMCs of the monkey that acquired SHIV was on average below the limit of quantification
- FTC-TP concentrations in PBMCs of this same monkey was within normal range.

FTC/TAF administered orally to macaques 24h before and 2h after vaginal virus exposure prevented SHIV infection to a degree similar to that previously reported with FTC/TDF, supporting the evaluation of FTC/TAF for PrEP in women.

Massud I, et al. CROI 2018, Boston, MA. Oral #85.

HIV Prevention in Cisgender Women: Safety and PK of a Potential New TAF-based PrEP Regimen

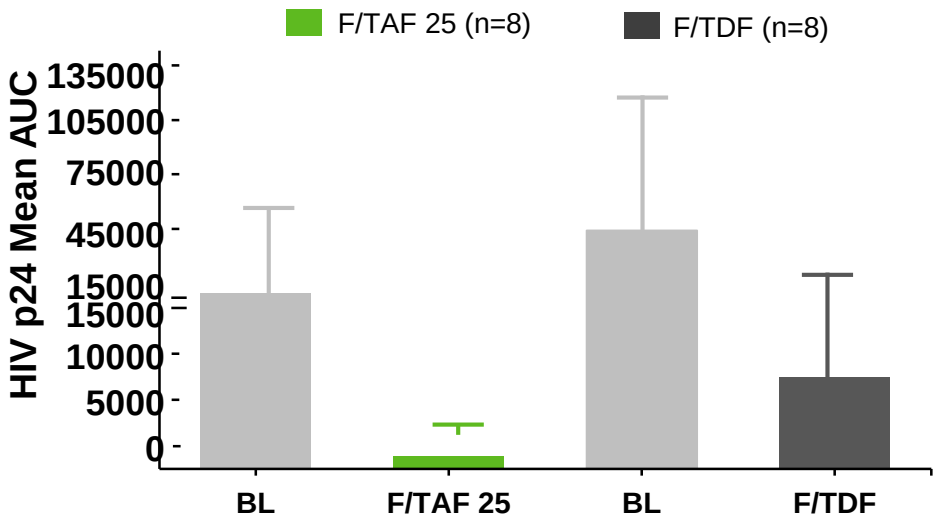
Phase I, prospective, randomized study to assess local and systematic PK, PD, and safety of daily oral FTC/TAF in healthy women over 8 months (N=75†)

- FTC/TAF 25 mg had lower plasma TFV than FTC/TDF (C_{max}=2.4, 6, and 314 ng/mL, respectively)
- FTC/TAF 25 mg had higher TFV-DP in PBMCs (C_{max}=74.4, 189, and 23.4 fmol/10^6 cells)
- In the women assigned to a biopsy 4 hours after 14 daily doses, FTC/TAF 25 mg had higher CV tissue TFV-DP levels than FTC/TDF

	F/TAF (200/25) N=24	F/TDF (200/300) N=25
Number (%) of women reporting at least one TEAE	**18 (75)**	**20 (80)**
Not product related	12 (67)	9 (45)
Product related	6 (33)	11 (55)
Number (%) of women reporting at least one Gastrointestinal TEAE*	**3 (13)**	**11 (44)**

- FTC/TAF 25 mg was shown to protect against HIV infection in an ex vivo tissue infection model

Cervical Tissue Infectivity Ex Vivo



These results show that FTC/TAF has fewer TEAE and is more potent ex vivo in cervical tissue compared to FTC/TDF, providing a foundation for future studies in women for PrEP.

CV, cervical and vaginal; PD, pharmacodynamics; PK pharmacokinetics; TEAE, treatment-emergent adverse events.
† Results for participants in F/TAF 10/200 arm not shown, n=26
* Nausea, diarrhea, vomiting, abdominal pain
Schwartz J, et al. HIVR4P 2018, Madrid, Spain. OA15.04

Gilead sNDA for Descovy for PrEP

sNDA and FDA Advisory Committee Discussion

- Gilead filed an sNDA for approval of Descovy for PrEP in April 2019 based on the results of the Discover study
- Gilead proposed a broad indication similar to Truvada including women and adolescents
- Gilead submitted an extrapolation report for women including the safety of Descovy for treatment of HIV, Phase 1 PK data, and preclinical monkey challenge data
- The FDA convened an Advisory Committee Meeting on August 6 2019 to consider the application

FDA Advisory Committee Discussion

- The Advisory Committee voted on 3 questions. Do the data presented support approval of Descovy for PrEP for:
- MSM and transgender women — Yes 16 No 2
- Cis gendered women — Yes 8 No 10
- Heterosexual men exposed by vaginal sex — No objection

Ongoing and Future Studies

Descovy for PrEP in women
Clinical Trials

- Phase 1
  - CONRAD 137 (completed)
- Phase 2/3
  - PrEPVacc (ongoing)
- Planned studies (in discussion)
  - Phase 3 efficacy trial of Descovy for PrEP in women (currently in discussion with the US FDA)
  - Studies in pregnant women
  - Studies in breast feeding women
  - Studies in adolescent women
  - Studies in women who inject drugs

Challenges in designing a phase 3 PrEP efficacy trial for Descovy in women

- It is not possible to conduct a large non-inferiority design similar to Discover
  - Difficult to construct a non-inferiority margin as efficacy data from placebo controlled studies of TVD are sparse
- Placebo controlled trials are ethically challenging; estimating placebo rates is challenging
- HIV incidence decreasing in some populations due to implementation of TASP
- Adherence to taking a daily pill (TVD) has been a challenge in previous studies (FEMPREP and VOICE)
- Perceived HIV risk is low in many populations
- For many women, avoiding HIV infection is not their highest priority

PrEPVacc: A Phase IIb three-arm, two-stage HIV prophylactic vaccine trial with a second randomization to compare TAF/FTC to TDF/FTC as pre-exposure prophylaxis

Jim Rooney, MD
on behalf of the PrEPVacc study team

MTN Meeting, Sep 2019

This project is part of the EDCTP2 Programme supported by the European Union

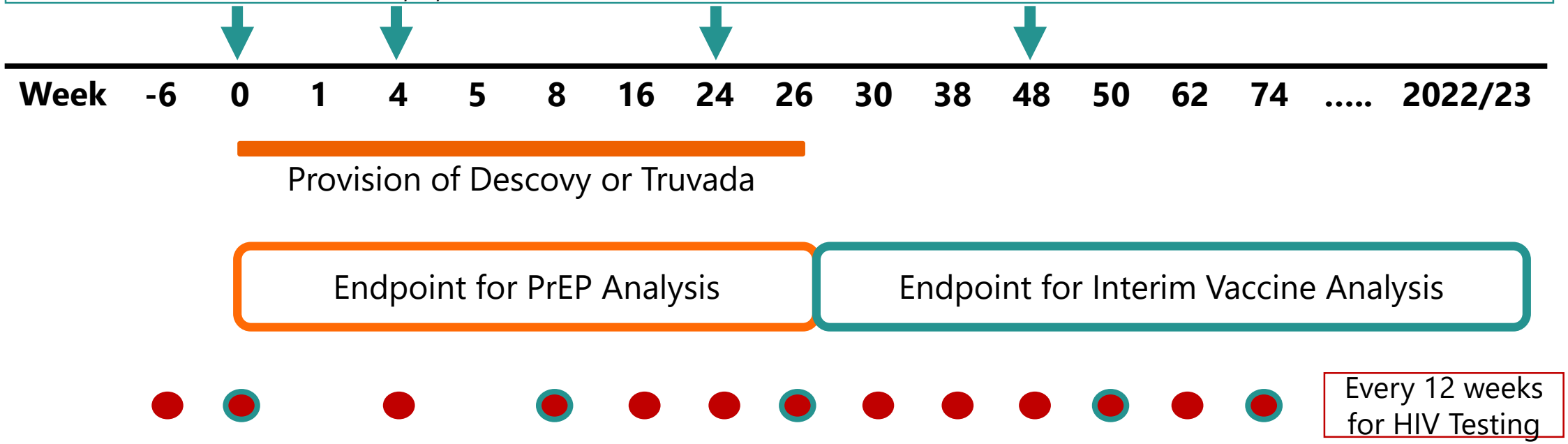
Object-ives

- To assess the safety and efficacy of two HIV-1 prophylactic vaccine regimens, each compared to placebo in reducing HIV incidence
- To compare the safety and effectiveness of Descovy (F/TAF) relative to Truvada (F/TDF) in reducing HIV incidence, in the context of background incidence

Study Schema

Vaccination

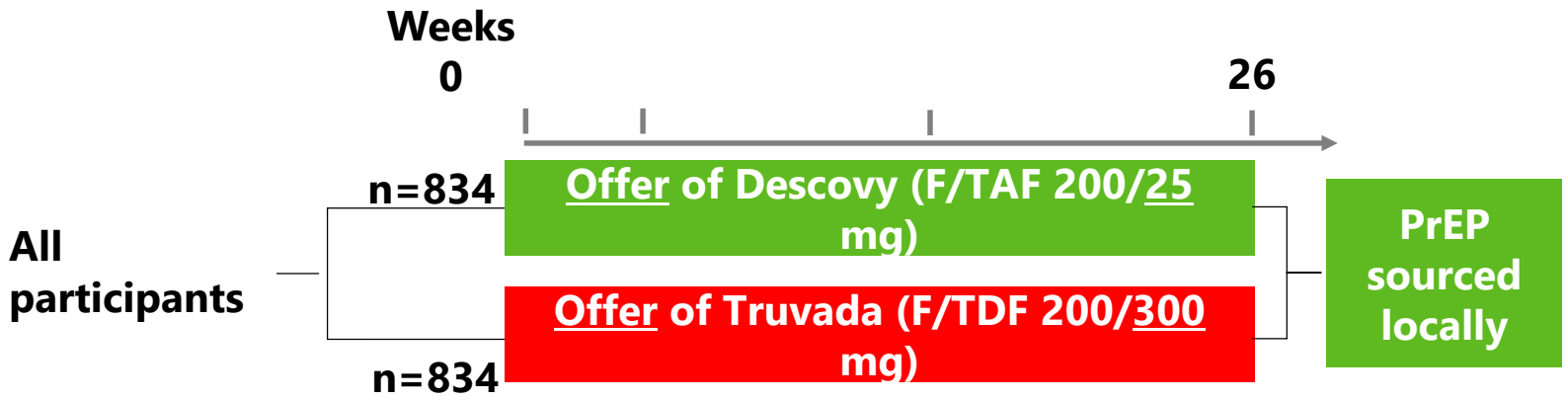
- **Arm A**: DNA-HIV-PT123 plus AIDSVAX B/E at Week 0, 4, 24 and 48
- **Arm B**: DNA-HIV-PT123 plus CN54gp140/MPLA at week 0 and 4, MVA-CMDR/CN54gp140/MPLA at week 24 and 48
- **Arm C**: Saline at week 0, 4, 24 and 48



PREP VACC

- Blood Draws. HIV testing/store are week -6, 0, 4, 8, 16, 24, 26, 30, 38, 48, 62, 74, every 12 week during LTFU
- Immunological Samples

PrEP Analysis



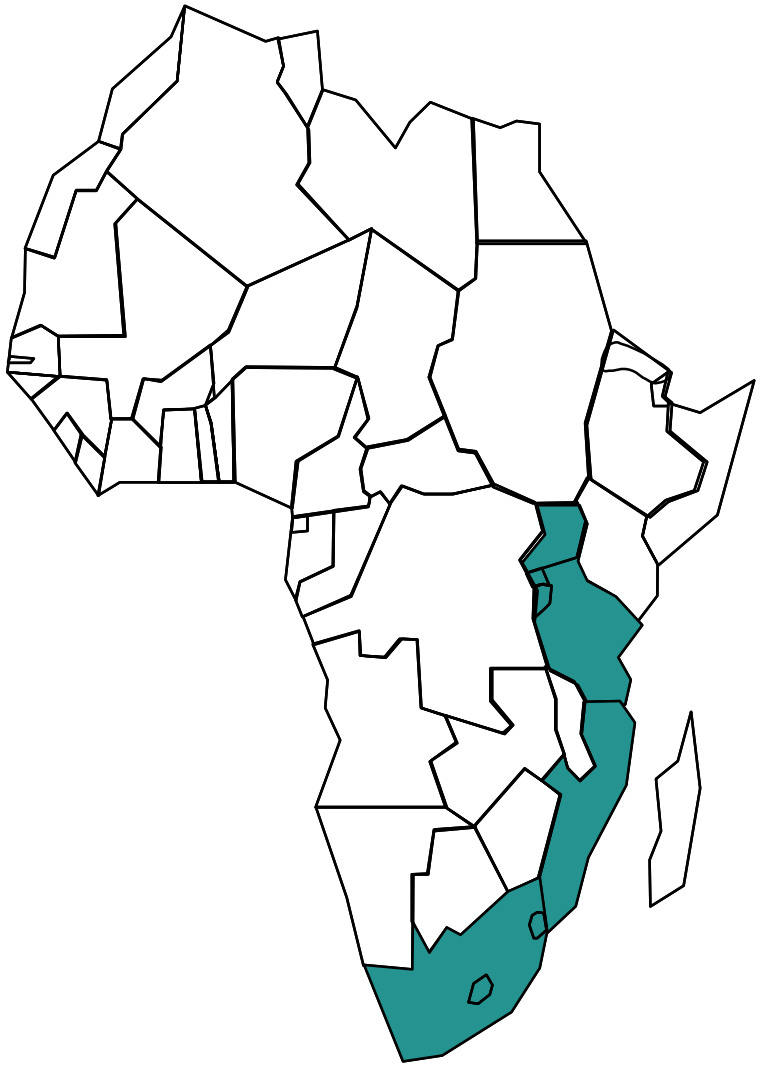
- Comparison of F/TAF to F/TDF needs to take account of background incidence (obtained through PrEPVacc registration cohort)

- **Averted Infections Ratio (AIR)** =

$$\frac{\text{incidence in cohort} - \text{incidence in Descovy}}{\text{Incidence in cohort} - \text{incidence in Truvada}}$$

Proportion of infections that are prevented by Descovy that would have been prevented by Truvada

The Averted Infections Ratio: a novel measure of effectiveness of experimental HIV pre-exposure prophylaxis agents. Lancet HIV. Vo5 June 2018



Trial Communities

- General population, MSM, Female Sex Workers, **Maputo**, **Mozambique**
- General population, **Durban, South Africa**
- Female bar workers, **Mbeya, Tanzania**
- Bar workers and Female Sex Workers, **Dar Es Salaam, Tanzania**
- Fisherfolk and key populations in **Masaka, Uganda**

PREP VACC

Registration Cohort: A Prospective, Longitudinal Observational Study

- To identify, recruit, and follow-up a cohort of male and female HIV-negative volunteers at high risk of HIV infection in preparation for the PrEPVacc trial
- To estimate incidence of HIV infection in the study volunteers
- To ascertain knowledge, perceptions, uptake of and adherence to PrEP (where it is available)
- To develop and refine key messages about HIV vaccines and PrEP as well as tools for conveying these messages.

PREP VACC

Enrollment Progress & Demogra-phics

	Masaka	Durban	Mbeya	Dar es Salaam	Maputo	Overall
Screened	479	235	184	773	105	**1776**
Enrolled	272	199	172	700	67	**1410**
% Female *(among enrolled)*	48%	55%	100%	100%	15%	**80%**
Age *(among enrolled)* *Mean(±SD)*	26 (±6.2)	24 (±4.6)	24 (±4.8)	27(±6.6)	25 (±6.5)	**26 (±6.1)**

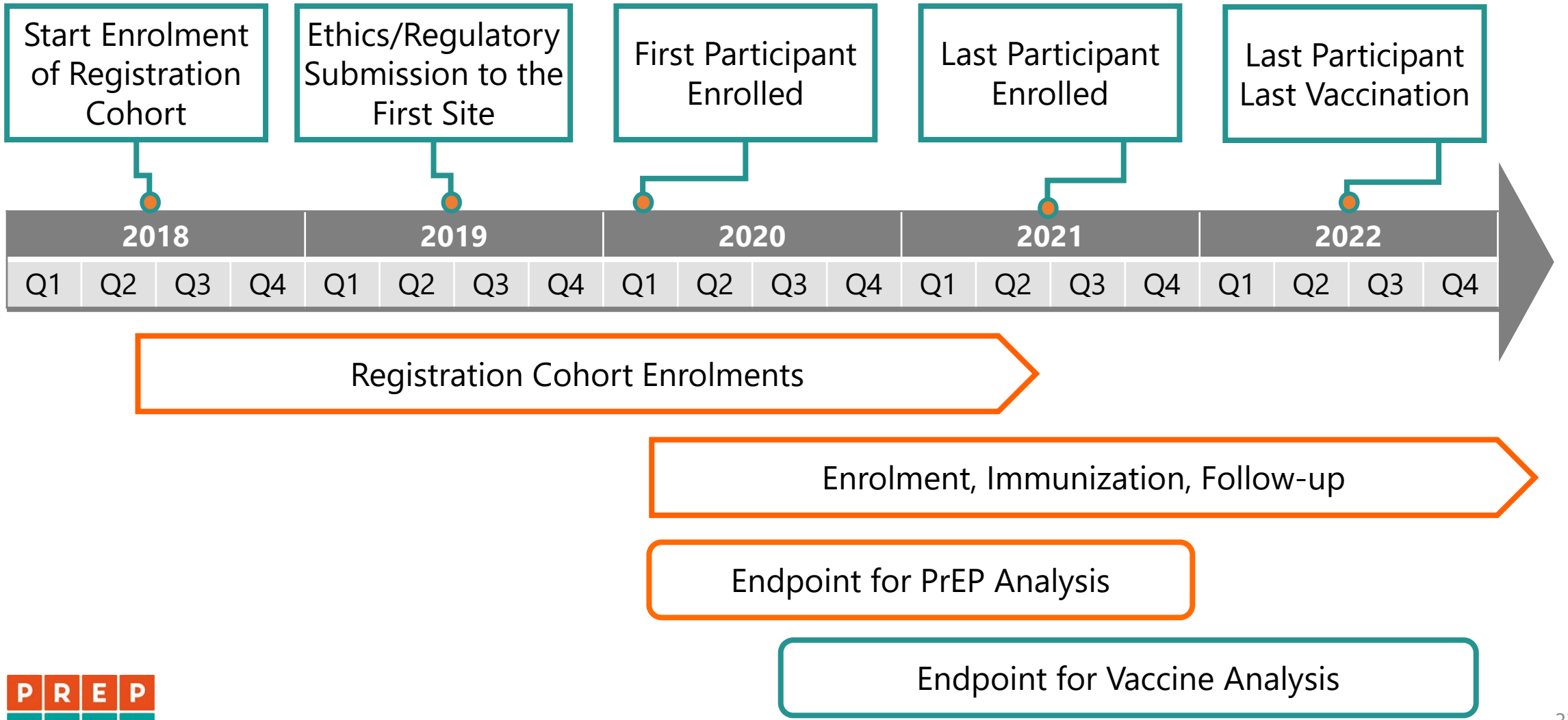
** Minimum age: 18 Maximum age: 45*

Data as of 16.05.2019

PrEP Knowledge and Uptake at baseline

	Masaka (n=272)	Durban (n=199)	Mbeya (n=172)	Dar es Salaam (n=700)	Maputo (n=67)	Overall (N=1410)
Heard about PrEP (%)	32	31	35	67	27	**49**
Using PrEP (%)	0	0	0	4	0	**3**
Willing to use PrEP (%)	73	81	94	98	93	**90**

Projected Timeline



PrEPVacc Summary

- Three trials in one – efficient and cost saving
  - High target vaccine efficacy of public health relevance
  - Will test each of two combination regimens compared to placebo
- Pragmatic approach to HIV vaccine trials in the era of PrEP
  - PrEP provided to support immunization phase
  - Opportunity for second randomization to assess Descovy in heterosexual population
  - Aspire to generate PrEP champions
  - Result will be relevant to programmatic roll-out
- Registration cohort key to achieving target incidence and timely accrual

PREP VACC

PrEPVacc Protocol Team

Sponsor:
Imperial College London
Jonathan Weber
Julie Fox/Cherry Kingsley

Coordinating Investigator:
MRC/UVRI&LSHTM
Pontiano Kaleebu
Eugene Ruzagira

MRC CTU at UCL
Sheena McCormack
Margaret Thomason

Statistics and Database
Christian Hansen/Sheila Kasiime/
Ayoub Kakande/Gertrude Mutonyi
(UVRI/LSHTM)
Angela Crook/David Dunn/
Henry Bern (UCL)

Laboratories
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Doug Taylor (FHI, IDMC Chair)

PrEPVacc Team

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Gilead Phase 3 study of Descovy for PrEP in women

- In discussion with FDA but design not finalized
- Efficacy study in women
- We were encouraged to propose new types of studies, and the study needs to provide convincing evidence of safety and efficacy
- To include at least two novel methods for estimating placebo incidence
- We hope to have a study outline by end of September
- PDUFA date is early October
- Prescribing information (label) including the indication and post marketing studies will be decided by then
- Additional non efficacy trials will also be conducted post approval

Gilead Phase 3 study of Descovy for PrEP in women

- We encourage anyone with creative thoughts about study design to reach out to us. Please contact me at jrooney@gilead.com and I would be happy to discuss with you. Or catch me at this meeting.
- In listening to and talking with various folks we have heard some interesting concepts
  - For populations with high incidence but low adherence, you could enrich for high adherers using a run in and measure drug levels. Select high adherers and then randomize (suggested by Jeff Murray in a talk in 2018)
  - For populations with low or intermittent adherence but high incidence, where you can measure drug levels, do monthly adherence levels and compare the incidence rates on and off drug (suggested in some form by Dave Glidden)
- No consensus at Gilead yet and no consensus with regulators; your ideas welcome

Gilead Phase 3 study of Descovy for PrEP in women

- Gilead is also looking for study sites that would be interested in participating in a study of Descovy for PrEP in women. If you are interested, please email me at jrooney@gilead.com and I can refer you to the right folks at Gilead who will collect additional information
- Eligible study sites should have
  - Experience in conducting studies of biomedical prevention
  - Population of high risk women with recent history of high incidence of infection
  - Be willing to collect data that can be used for regulatory submission
- Gilead will ask for information related to past clinical trial experience, the demographics of the high risk population, and any information regarding recent measurements of incidence, as well as target enrollment capabilities

Thank You!!!!

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