Using the F/TDF Adherence-Efficacy Relationship to Calculate Background HIV Incidence: Results From the DISCOVER Trial

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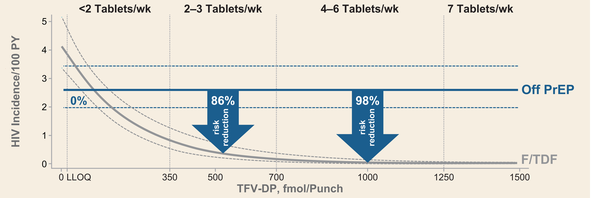
Introduction

- Adherence to oral emtricitabine/tenofovir disoproxil fumarate (F/TDF) is strongly correlated with its efficacy in HIV pre-exposure prophylaxis (PrEP)[1]
- Notably, the relationship between objective measures of adherence—as measured by tenofovir diphosphate (TFV-DP)—and HIV prevention efficacy is well characterized[2]

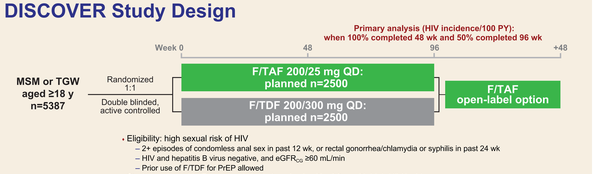
TFV-DP Levels in DBS and HIV Incidence*



*Adapted from Grant et al.[2] DBS, dried blood spot; LLOQ, lower limit of quantitation; PY, person-years.

- The DISCOVER trial (NCT02842086), a double-blinded, randomized, active-controlled trial, demonstrated the noninferiority of emtricitabine/tenofovir alafenamide (F/TAF) to F/TDF: HIV incidence rate ratio 0.47 (95% confidence interval [CI] 0.19, 1.15)[3]

DISCOVER Study Design



- Eligibility: high sexual risk of HIV
  - 2+ episodes of condomless anal sex in past 12 wk, or rectal gonorrhea/chlamydia or syphilis in past 24 wk
  - HIV and hepatitis B virus negative, and $eGFR_{CG}$ ≥60 mL/min
  - Prior use of F/TDF for PrEP allowed
- Study conducted in Europe and North America in cities/sites with high HIV incidence

$eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; MSM, men who have sex with men; TGW, transgender women.

- The DISCOVER trial did not have a placebo arm, and therefore, there are no data on HIV incidence in a counterfactual population similar to the study participants, but not receiving PrEP; thus it was not possible to calculate the prevention efficacy of F/TAF or F/TDF, nor the number of treated people needed to prevent HIV infection

Objectives

- To use the well-characterized adherence-efficacy relationship for F/TDF to:
  - Back-calculate the counterfactual (non-PrEP) background HIV incidence (bHIV) in the F/TDF arm of DISCOVER under varying sets of assumptions
  - Use this estimate of bHIV to calculate the prevention efficacy of F/TAF and F/TDF
  - Calculate the number needed to prevent HIV for each drug

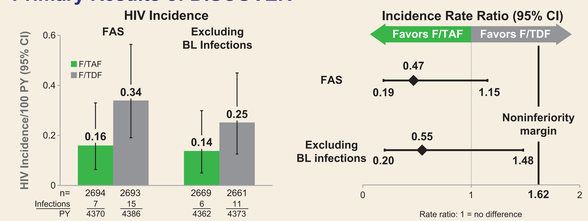
Methods

- TFV-DP levels in DBS were assessed for all participants diagnosed with HIV and in a randomized subset of 10% in DISCOVER
- We used a Bayesian model with a prior distribution, derived from iPrEx open-label extension (OLE), relating TFV-DP levels to HIV prevention efficacy, eg, TFV-DP levels of 350 (low), 350–<700 (medium), and ≥700 (high) fmol/punch were assumed to provide 0%, 86%, and 98% HIV protection, respectively
- A flat prior, combined with the F/TDF seroconversion rate and TFV-DP levels, permits Bayesian inferences on the estimate of the counterfactual bHIV
- Sensitivity analyses included:
  - Drug level prior informed by incorporating suspected baseline (BL) HIV infections
  - Skeptical prior incorporated a low estimate of bHIV in DISCOVER, a conservative assumption to address concerns that DISCOVER had a low bHIV due to the recruitment of low-risk individuals
  - Potential confounding between study drug adherence and risk behavior was addressed by assuming that participants with low adherence also had 9-fold higher risk behavior
- Using these different bHIV estimates, we calculated:
  - HIV prevention efficacy of F/TAF and F/TDF
  - Number of averted HIV infections on either drug
  - Number of people needed on either drug to prevent 1 new HIV infection
- RStan was used to sample 10,000 realizations from the posterior distribution

Results

- For demographics and BL characteristics of DISCOVER participants, see Mayer et al[3]

Primary Results of DISCOVER



Study Arm	Randomized, n	Exposure, PY	Total HIV+, n	Postenrollment HIV+, n	Postenrollment HIV Rate/100 PY
F/TAF	2694	4370	7	6	0.138
F/TDF	2693	4386	15	11	0.252

CI, confidence interval; FAS, full analysis set.

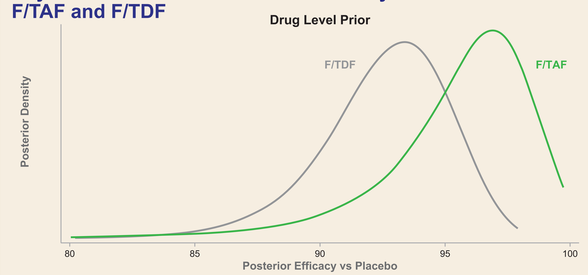
Distribution of HIV Infections and Person-Time in DISCOVER F/TDF Arm by TFV-DP DBS Adherence Category

TFV-DP in DBS, fmol/Punches	iPrEx OLE[2]			F/TDF Arm of DISCOVER	
	Average Adherence*	Relative Risks vs Placebo (95% CI)	HIV Prevention Efficacy, %	Acquired Infections, n	Estimated PY in Case Cohort (%)†
<350	Low: <2 tablets/wk	1.19 (0.76, 1.87)	0	10	219 (5)
350–<700	Moderate: 2–3 tablets/wk	0.14 (0.02, 0.76)	86	0	395 (9)
≥700	High: ≥4 tablets/wk	0.02 (0.00, 0.49)	98	1	3772 (86)

*Over previous month; †Estimated from design of case-cohort study and Bayesian model.

- High adherence was observed in most of the person-time in the DISCOVER F/TDF arm (86%) and there was only 1 infection in this category
- Low adherence was observed in only 5% of the person-time; however, 91% of the HIV infections occurred in this category
- There were no infections among the 9% of person-time with moderate adherence

Bayesian Estimates of Posterior Efficacy Distributions for F/TAF and F/TDF

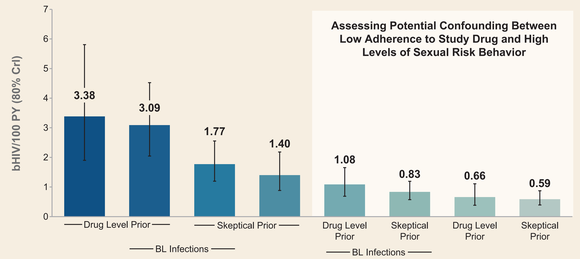


- If we chose a prior distribution based on drug levels, ie, estimating the counterfactual bHIV using only the F/TDF adherence-efficacy relationship distribution for bHIV, the Bayesian model yielded a median posterior bHIV (80% credible interval [CrI]) of 3.4 (1.9, 5.9)/100 PY, which suggests a median efficacy (95% CrI) of 96% (88%, 99%) for F/TAF and 93% (87%, 96%) for F/TDF

Calculating HIV Incidence Based on Suspected Baseline HIV Infections

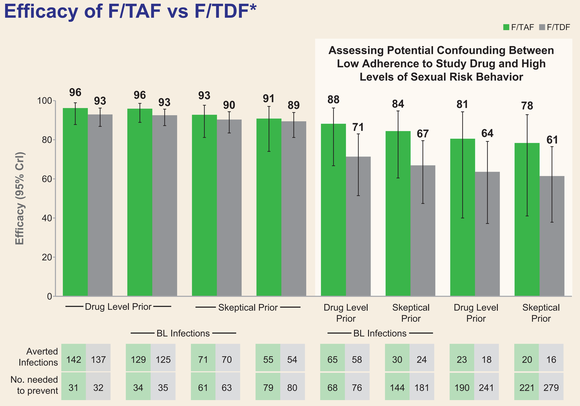
- In DISCOVER, there were 5 participants who appeared to have acquired HIV within an average of a month between their negative screening HIV test and subsequent positive test
- Assuming a 14-d average lag time between infection and a positive test, this leads to the estimation that the 5 infections were observed over ~173 PY of possible follow-up
- Based on this assumption, the bHIV estimate based on the 5 suspected BL HIV infections was 2.9 (95% CI 0.9, 6.7)/100 PY
  - This is likely an underestimate of the true counterfactual bHIV in the participant population as most individuals were screened and only referred to DISCOVER once they were confirmed to be HIV negative

Estimates of the DISCOVER Counterfactual bHIV by Adherence-Efficacy Method Under Varying Assumptions



- The highest bHIV estimate comes from the drug level prior that only used data from the adherence-efficacy relationship to predict the counterfactual bHIV
- As increasingly conservative information was added, eg, data from the BL infections that may have underestimated bHIV or a skeptical prior with a low bHIV, assuming individuals with limited sexual risk were enrolled in DISCOVER, the estimates of bHIV fell
- Lastly, we explored the role of confounding between study drug adherence behavior and sexual risk behavior by adding this confounding sensitivity analyses to the scenarios in the right panels of the above and below graphs

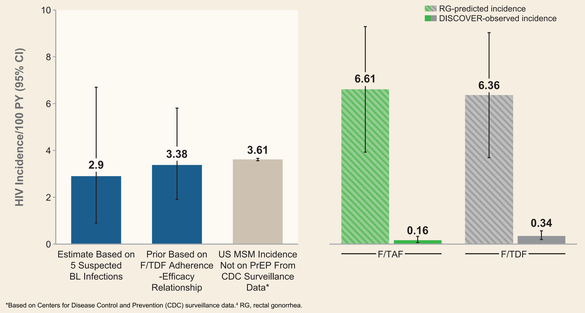
Efficacy of F/TAF vs F/TDF*



*Estimates of efficacy of F/TAF and F/TDF for each Bayesian estimate of bHIV, and corresponding estimates of number of averted infections and number of treated persons needed to prevent 1 infection for both F/TAF and F/TDF are shown.

- As bHIV estimates decreased, the differential in efficacy estimates increased between F/TAF and F/TDF

Comparing Counterfactual Estimates of Background Placebo HIV Incidence



*Based on Centers for Disease Control and Prevention (CDC) surveillance data.[4] RG, rectal gonorrhea.

- The bHIV estimate by the drug level prior, eg, the F/TDF adherence-efficacy relationship alone, provided a point estimate of incidence that was similar to those estimates calculated by the BL HIV infection estimate and the US MSM HIV incidence counterfactual estimate from CDC surveillance data[4]
- The 3 estimates of bHIV on the left are similar
- Another method for calculating counterfactual bHIV, using the correlation between rectal gonorrhea and HIV incidence, appears to overestimate the bHIV; this is likely due to establishment of the correlation earlier in the epidemic and a change in the relationship as more people with HIV are treated and virologically suppresed, and with greater uptake of PrEP in the community

Conclusions

- We used data from the DISCOVER trial to demonstrate how Bayesian models utilizing the well-characterized F/TDF adherence-efficacy relationship can estimate the following:
  - Counterfactual background HIV incidence in the F/TDF arm of the study (3.4/100 PY)
  - High efficacy of both F/TAF (96%) and F/TDF (93%) based on the estimate of BL HIV incidence
  - Estimated number of HIV infections averted by F/TAF (142) and F/TDF (137)
  - Number needed to receive PrEP to prevent 1 new HIV infection for both F/TAF (31) and F/TDF (32)
- The Bayesian models exploring different assumptions regarding the background HIV incidence (if it were lower than expected), adding data from DISCOVER on the incidence of BL HIV infections, provided relatively similar and high estimates of efficacy for both F/TAF and F/TDF
  - Exploring confounding (assuming those with low adherence had 9-fold higher risk behavior) added to each of the models, suggesting that F/TAF may have higher efficacy than F/TDF, with lower bHIV incidence estimates
- This estimate of background HIV incidence (3.4/100 PY) by the Bayesian method is consistent with the DISCOVER estimate using BL HIV infection incidence (2.9/100 PY) and estimated HIV incidence using CDC surveillance data for new diagnoses in MSM not on PrEP (3.6/100 PY)
- New HIV prevention trials cannot include a placebo arm for ethical reasons. Including F/TDF as the internal active control provides a built-in counterfactual placebo arm, which allows the estimation of background HIV incidence and measures of new PrEP drug efficacy

References: **1.** Grant RM, et al. N Engl J Med 2010;363:2587-99; **2.** Grant RM, et al. Lancet Infect Dis 2014;14:820-9; **3.** Mayer K, et al. Lancet 2020;396:P239-54; **4.** Mera R, et al. J Int AIDS Soc 2019;22:e25433. **Acknowledgments:** We extend our thanks to the participants, their families, and all participating study investigators and staff: *Austria:* B Haas, A Rieger; *Canada:* J Brunetta, JJ de Wet, J Szabo, C Tremblay, B Trottier; *Denmark:* J Gerstoft, G Kronborg, C Larsen, D Lamers; *France:* E Cua, J-M Molina, P Philibert, G Pialoux; *Germany:* H Jessen, G Knuchl, I Kromanic, C Spinner; *Ireland:* C Bergin, P Mallon; *Italy:* A Antinori, A Lazzarin; *Netherlands:* M Prins; *Spain:* J Coll, M Crespo, J del Romero Gerrero, D Podzamczer; *UK:* V Apea, A Clarke, O Dosekun, R Gilson, S Kegg, C Leen, N Nwokolo, F Post, I Reeves, G Schembri, S Taylor; *USA:* D Asmuth, A Avery, P Benson, M Berhe, I Brar, C Brinson, JH Burack, T Campbell, M Cespedes, M Coleman, CM Creticos, GE Crofoot, FA Cruickshank, E Daar, E DeJesus, W Dirges, S Dolekicki-Lewis, T Donovan, J Flamm, JE Gallant, J Gladstein, RM Grant, R Grossberg, J Halperin, WD Hardy, CB Hare, S Hassler, R Hengel, K Henry, T Hodge, S Hosek, M Iandorio, A LaMarca, C Lucasi, S Mannheimer, CT Martorell, M Markowitz, K Mayer, A Mills, S Morris, K Mounzer, O Ogbuagu, O Osiyemi, A Petrol, J Phoenix, MN Ramgopal, B Rashbaum, GJ Richmond, PJ Ruane, L Salazar, AJ Scarsella, M Scott, P Shalit, JL Stephens, MA Thompson, G Voskuhl, BH Wade, DA Wohl, K Workowski, B Young. This study was funded by Gilead Sciences, Inc.