# Tenofovir Alafenamide vs Tenofovir DF in Women: Pooled Analysis of 7 Clinical Trials

**Melanie A. Thompson,[1] Indira Brar,[2] Cynthia Brinson,[3] Catherine M. Creticos,[4] Debbie Hagins,[5] Ellen Koenig,[6] Claudia T. Martorell,[7] Cristina Mussini,[8] Laura Waters,[9] Susan Guo,[10] Ya-Pei Liu,[10] Lauren Temme,[10] Devi SenGupta,[10] Moupali Das[10]**

[1]AIDS Research Consortium of Atlanta, Georgia, USA; [2]Henry Ford Health System, Detroit, Michigan, USA; [3]Central Texas Clinical Research, Austin, Texas, USA; [4]Howard Brown Health, Chicago, Illinois, USA; [5]Chatham County Health Dept, Savannah, Georgia; [6]Instituto Dominicano de Estudios Virológicos–IDEV, Santo Domingo, República Dominicana; [7]Infectious Diseases and The Research Institute, Springfield, Massachusetts, USA; [8]Azienda Ospedaliera–Universitaria di Modena, Italy; [9]Mortimer Market Centre, London, UK; [10]Gilead Sciences, Inc, Foster City, California, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

## Introduction

- Globally, the majority of people living with HIV (PLH) are cis-women, and the number of women acquiring HIV infection continues to rise[1]
- Research guidelines have long advocated for sex-based assessment of drug efficacy, toxicity, and tolerability profiles, but women continue to be underrepresented in clinical trials assessing efficacy and safety of antiretroviral treatment (ART) among PLH[2,3]
- One of the consequences of this restricted representation is the absence of definitive information about the specific efficacy and safety of ART in women[4-10]
- Tenofovir alafenamide (TAF) has demonstrated an improved renal and bone safety profile relative to tenofovir disoproxil fumarate (TDF) in multiple randomized trials with similar efficacy[11-15]

## Objective

- To evaluate the efficacy and safety of TAF vs TDF for ART initiation or switch in cis-women in a pooled analysis of 7 studies (only including cis-women, referred to as women herein), and to compare outcomes to those in men

## Methods

### Studies Included in Integrated Analysis

**779 women from 7 (5 double-blind, 2 open-label) randomized studies***

| | | |
|---|---|---|
| 292-0104 | N=867 | E/C/F/TAF vs E/C/F/TDF |
| 292-0111 | N=866 | E/C/F/TAF vs E/C/F/TDF |

**Treatment Naïve (n=2 studies, 260 women)**

| | | |
|---|---|---|
| 380-1878 OL | N=577 | B/F/TAF vs boosted PI -regimens |
| 366-1160 | N=875 | FTC/RPV/TAF vs EFV/FTC/TDF |
| 366-1216 | N=630 | FTC/RPV/TAF vs FTC/RPV/TDF |
| 311-1089 | N=663 | F/TAF + 3rd agent vs F/TDF + 3rd agent |
| 292-0109 OL | N=1436 | E/C/F/TAF vs TDF -containing regimens |

**Virologically Suppressed (n=5 studies, 519 women)**

**Outcomes**

- Efficacy (Snapshot analysis)
- Safety
  - Overall (most common AEs)
  - Renal
    - AEs, AEs leading to discontinuation, cases of proximal renal tubulopathy or Fanconi syndrome
    - eGFR by Cockcroft-Gault (CrCl; mL/min)
    - Glomerular proteinuria (UACR), tubular proteinuria (urine RBP:Cr and β2M:Cr)
  - Bone (BMD)

*Individual studies were not powered to evaluate outcomes by sex. AE, adverse event; B, BIC; bictegravir; BMD, bone mineral density; β2M, β2-macroglobulin; C, cobicistat; CrCl, creatinine clearance; E (or EVG), elvitegravir; EFV, efavirenz; eGFR, estimated glomerular filtration rate; F (and FTC), emtricitabine; PI, protease inhibitor; RBP, retinol-binding protein; R, RPV, rilpivirine; SCr, serum creatinine; UACR, urine albumin creatinine ratio.

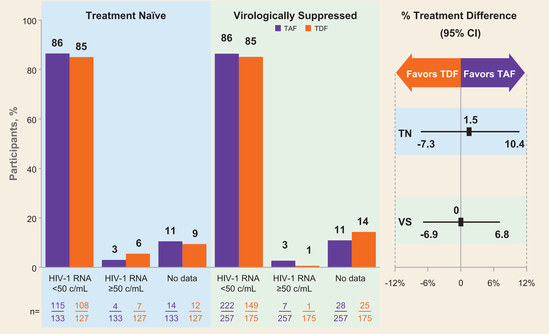
## Results

### Baseline Characteristics

| | | Treatment Naïve | | Virologically Suppressed | |
|---|---|---|---|---|---|
| | | TAF (n=133) | TDF (n=127) | TAF (n=296) | TDF (n=223) |
| Median age, y (range) | | 37 (19, 66) | 40 (18, 63) | 47 (22, 73) | 47 (22, 69) |
| Race/ethnicity, % | Black or African descent | 38 | 32 | 48 | 53 |
| | Hispanic/Latina ethnicity | 24 | 27 | 25 | 24 |
| Region, % | US | 38 | 42 | 72 | 74 |
| | Ex-US | 62 | 58 | 28 | 26 |
| Median body mass index, kg/m² (IQR) | | 25 (22, 31) | 26 (22, 31) | 29 (24, 34) | 27 (24, 32) |
| Median HIV-1 RNA, $\log_{10}$ c/mL (IQR) | | 4.5 (4, 5) | 4.5 (4, 5) | — | — |
| Median CD4 cell count, cells/μL (IQR) | | 358 (243, 480) | 367 (276, 450) | 726 (578, 909) | 689 (508, 909) |
| Median $eGFR_{CG}$, mL/min (IQR) | | 116 (91, 136) | 104 (89, 129) | 107 (87, 128) | 100 (77, 121) |
| Medical history, % | Diabetes mellitus | 6 | 10 | 9 | 7 |
| | Hypertension | 17 | 19 | 34 | 30 |
| | Cardiovascular disease | 2 | 0 | 4 | 1 |
| | Hyperlipidemia | 7 | 13 | 36 | 25 |

c, copies; IQR, interquartile range.

## Virologic Outcomes at Week 96 by FDA Snapshot




CI, confidence interval; FDA, Food and Drug Administration; TN, treatment naïve; VS, virologically suppressed.

- Of treatment naïve men, 87% on TAF and 85% on TDF achieved HIV-1 RNA <50 c/mL at Week 96; suppression was maintained in 91% of virologically suppressed men on TDF vs 89% on TAF
- **Efficacy results were similar for TAF vs TDF in both women and men**

## Most Common AEs in Treatment Naïve Women Through Week 144

| n (%) | TAF (n=133) | TDF (n=127) |
|---|---|---|
| Nausea | 24 (18) | 40 (31) |
| Nasopharyngitis | 30 (23) | 32 (25) |
| Headache | 28 (21) | 28 (22) |
| URTI | 26 (20) | 27 (21) |
| Diarrhea | 29 (22) | 21 (17) |
| Arthralgia | 23 (17) | 21 (17) |
| Urinary tract infection | 18 (14) | 20 (16) |
| Dizziness | 16 (12) | 19 (15) |
| Back pain | 16 (12) | 18 (14) |
| Vaginal discharge | 16 (12) | 14 (11) |
| Vomiting | 15 (11) | 14 (11) |
| Osteopenia | 16 (12) | 10 (8) |
| Abdominal pain | 14 (11) | 4 (3) |

URTI, upper respiratory tract infection.

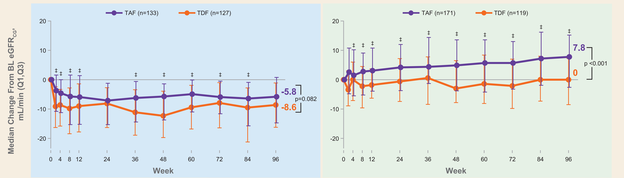
- Incidence of individual AEs in women was similar for TAF vs TDF, and consistent with men
- Discontinuation due to AE/death was 0% on TAF vs 1.6% on TDF in treatment naïve women and 1.3% (TAF) vs 2.2% (TDF) in virologically suppressed women through Week 96
- **TAF was well-tolerated in women with a similar overall safety profile for TAF and TDF, and consistent with data in men**

## Treatment Naïve — Virologically Suppressed

### Changes in Bone Mineral Density (BMD) Through Week 96


- In treatment naïve men, median % change in BMD was -1.0 on TAF and -2.8 on TDF (spine)* and -0.8 on TAF and -3.5 on TDF (hip)* at Week 96
- In virologically suppressed men, these values were 1.8 for TAF vs 0 for TDF (spine)* and 1.8 for TAF vs -0.5 for TDF (hip)*
- **Women initiating TAF had less BMD decline vs TDF, and women switching to TAF from TDF had improvements in BMD; similar to results in men**

### Changes From Baseline in $eGFR_{CG}$ Through Week 96†

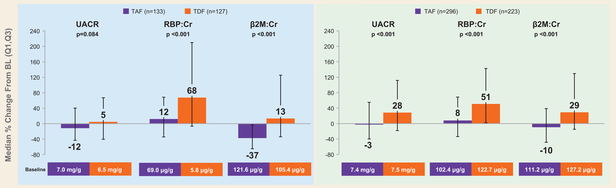



- In treatment naïve men, median change in $eGFR_{CG}$ was -4.7 mL/min on TAF and -8.0 on TDF‡; in virologically suppressed men, median eGFR increased by 5.8 mL/min with switch to TAF vs 0.7 staying on TDF‡
- **Women initiating TAF had numerically less eGFR decline vs TDF, and women switching to TAF from TDF had improvements in eGFR, consistent with data in men**

*p <0.001, calculated from analysis of variance model including study and treatment as fixed effects for BMD; †Virologically suppressed group excluded women who switched from EFV/FTC/TDF; ‡Significant treatment difference between TAF and TDF (calculated from 2-sided Wilcoxon rank-sum test). Q, quartile.

## Treatment Naïve — Virologically Suppressed

### Changes From Baseline in Renal Biomarkers at Week 96




- In treatment naïve men, median % change (TAF vs TDF) in UACR was -4 vs 5*; RBP:Cr was 14 vs 75*; β2M:Cr was -30 vs 37*
- In virologically suppressed men, median % change (TAF vs TDF) in UACR was -6 vs 27*; RBP:Cr was -3 vs 62*; β2M:Cr was -30 vs 55*
- **Women initiating or switching to TAF had less tubular proteinuria (RBP:Cr, β2M:Cr) vs TDF, similar to results in men**

*p <0.001, calculated by Wilcoxon rank-sum test.

### Treatment-Emergent Renal AEs at Week 96

| | Treatment Naïve | | | Virologically Suppressed | | |
|---|---|---|---|---|---|---|
| TEAE, n (%) | TAF (n=133) | TDF (n=127) | p-value | TAF (n=296) | TDF (n=223) | p-value |
| Renal and urinary disorders | 5 (4) | 10 (8) | 0.19 | 14 (5) | 14 ( 6) | 0.44 |
| Dysuria | 1 (1) | 2 (2) | | 3 (1) | 4 (2) | |
| Proteinuria | 2 (2) | 3 (2) | | 4 (1) | 3 (1) | |
| Hematuria | 1 (1) | 4 (3) | | 2 (1) | 2 (1) | |
| Pollakiuria | 1 (1) | 0 | | 3 (1) | 1 (<1) | |
| Oliguria | 0 | 2 (2) | | — | — | |
| Renal failure | 0 | 1 (1) | | — | — | |
| Acute kidney injury | — | — | | 0 | 2 (1) | |
| Chronic kidney disease | — | — | | 1 (<1) | 1 (<1) | |
| Chromaturia | — | — | | 1 (<1) | 0 | |
| Leukocyturia | — | — | | 1 (<1) | 0 | |
| Polyuria | — | — | | 0 | 1 (<1) | |
| Sterile pyuria | — | — | | 0 | 1 (<1) | |
| **TEAEs leading to drug discontinuation** | | | | | | |
| Renal and urinary disorders | 0 | 1 (1) | 0.31 | 0 | 1 (<1) | 0.43 |
| Chronic kidney disease | 0 | 0 | | 0 | 1 (<1) | |
| Renal failure | 0 | 1 (1) | | 0 | 0 | |

TEAE, treatment-emergent adverse event.

- In women, there were no cases of proximal renal tubulopathy or Fanconi syndrome with TAF vs 1 with TDF*; in men there were 0 cases with TAF vs 9 with TDF

*E/C/F/TDF.

## Conclusions

- Cis-women who initiated or switched to TAF had significantly improved BMD and renal tubular biomarkers compared to those on TDF, with similar rates of virologic suppression through Week 96
- Results were similar to those in men
- These pooled data from 7 studies demonstrate a safety advantage for initiating therapy with or switching to TAF compared to TDF in women

**References:** **1.** Global report: UNAIDS report on the global AIDS epidemic 2013. http://files.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf. **2.** Bennett JC, et al. N Engl J Med 1993;329:288-92. **3.** Sherman LA, et al. Science 1995;26:793-5. **4.** Currier J, et al. Ann Intern Med 2010;153:349-57. **5.** d'Arminio Monforte A, et al. AIDS 2010;24:1091-4. **6.** Hodder S, et al. HIV Med 2012;13:406-15. **7.** Monforte A, et al. Antivir Ther 2013;18:27-34. **8.** Soon GG, et al. AIDS Patient Care STDs 2012;26:444-53. **9.** Squires K, et al. Lancet HIV 2015;2:e407-16. **10.** Umeh OC, et al. Expert Opin Metab Toxicol 2006;2:273-83. **11.** Arribas JR, et al. J Acquir Immune Defic Syndr 2017;75:217-8. **12.** Daar E, et al. Lancet HIV 2018;5:e347-56. **13.** Duicescu E, et al. Adv Res Hum Retroviruses 2018;34:337-42. **14.** Hagins D, et al. HIV Med 2018;19:724-33. **15.** Raffi F, et al J Acquir Immune Defic Syndr 2017;75:226-31.

**Acknowledgments:** We extend our thanks to the women, their partners and families, and all investigators and study staff for GS-US-292-0104, 292-0111, 292-0109, 311-1089, 366-1160, 366-1216, and 380-1878. Special thanks to the Gilead study teams. These studies were funded by Gilead Sciences, Inc.