PE8/3

Bone and Renal Safety of Switching to Rilpivirine / Emtricitabine / Tenofovir Alafenamide (RPV/FTC/TAF) from Single-Tablet Regimens (STRs) Containing Efavirenz / Emtricitabine / Tenofovir Disoproxil Fumarate (EFV/FTC/TDF) or Rilpivirine / Emtricitabine / Tenofovir Disoproxil Gumarate (RPV/FTC/TDF): Week 48 Subgroup Analysis in Patients at Risk of or with Comorbidities

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Background

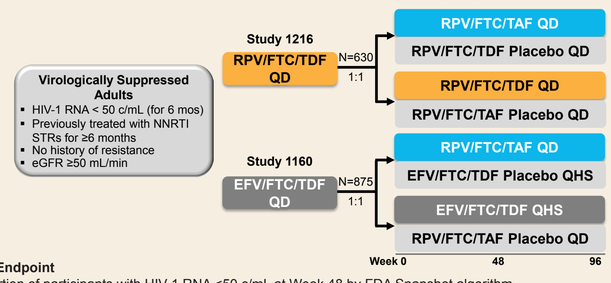
- Tenofovir alafenamide (TAF) is a novel tenofovir prodrug that achieves 91% lower plasma tenofovir levels than with TDF, reducing renal and bone toxicity.
- RPV/FTC/TAF is safe and well tolerated and may provide benefit to older adults and individuals with pre-existing comorbidities.
- Week 48 primary endpoint results of the pooled studies (1216 and 1160) were reported at a conference in 2016 and published separately in Lancet HIV
  - Orkin C, et al. HIV Drug Therapy 2016. Glasgow, UK. O124
  - Orkin C, et al. Lancet HIV 2017;4(5):e195-e204
  - DeJesus E, et al. Lancet HIV 2017;4(5):e205-e213

Methods

- Virologically suppressed (HIV-1 RNA <50 c/mL), HIV-infected adults taking RPV/FTC/TDF (Study 1216) or EFV/FTC/TDF (Study 1160) for ≥6 months were randomized to switch to RPV/FTC/TAF or continue their original NNRTI STR in two double-blind, active-controlled, phase 3 studies.
- This post hoc analysis evaluates tolerability, bone and renal safety, and lipid profile by age (above/below 50yrs), sex, and presence of preexisting diabetes, hypertension and hyperlipidemia.
- Treatment arms were pooled for switched to RPV/FTC/TAF vs. continued original NNRTI STR, except for lipid and some renal (serum creatinine) analyses where the individual studies were evaluated.

Study Design*

Two separate Phase 3b, 96-week, randomized, double-blind, active-controlled studies evaluating switch from RPV/FTC/TDF or EFV/FTC/TDF to RPV/FTC/TAF in virologically suppressed adults



Primary Endpoint
- Proportion of participants with HIV-1 RNA <50 c/mL at Week 48 by FDA Snapshot algorithm

Secondary Endpoints
- Change from baseline in CD4+ and BMD (hip and spine) at Weeks 48 & 96
- Proportion of participants with HIV-1 RNA ≥50 c/mL at Weeks 48 and 96 and HIV-1 RNA <50 c/mL at Weeks 96 by FDA Snapshot algorithm

* Dietary counselling
- RPV STRs/placebo with food (no restrictions specified)
- EFV STRs/placebo without food

Results

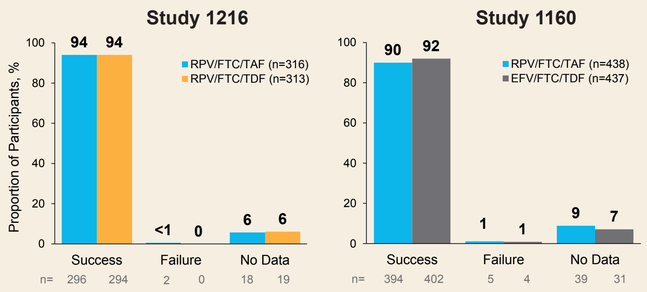
Table 1. Pooled Baseline Demographics & Disease Characteristics

	Studies 1216 & 1160			
	RPV/FTC/TAF		(EFV or RPV)/ FTC/TDF	
	≥50 yrs (N=324)	< 50 yrs (N=430)	≥50 yrs (N=300)	< 50 yrs (N=451)
Median age, years (range)	55 (50-74)	41 (21-49)	54 (50-76)	41 (19-49)
Male	83%	88%	87%	93%
Race/ethnicity				
White	74%	67%	72%	69%
Black or African descent	22%	26%	25%	22%
Latino/Hispanic	14%	17%	14%	20%
Median $eGFR_{CG}$, mL/min (range)	98 (54-195)	113 (57-239)	95 (46-189)	111 (49-265)
Dipstick proteinuria - Grade 1*	9%	7%	9%	8%
Diabetes mellitus	7%	2%	10%	1%
Hypertension	36%	15%	37%	14%
Hyperlipidemia	44%	27%	48%	24%

* There are no Grade 3 proteinuria in either study; only 1 and 3 participants had baseline Grade 2 proteinuria in Studies 1216 and 1160, respectively.
eGFR: estimate glomerular filtration rate

- Older participants (≥ 50 years) represented 41% of the pooled study population and had approximately 2-fold higher rates of comorbid conditions (diabetes, hypertension, and hyperlipidemia) compared to younger participants (Table 1).
- 46% of participants had at least one of the pre-existing condition of interest - diabetes (4%), hypertension (24%), and hyperlipidemia (34%). Participants with these pre-existing conditions were more likely to have the other comorbid conditions:
  - Diabetics (n=65): Hypertension (74%) and hyperlipidemia (72%)
  - Hypertensives (n=361): Hyperlipidemia (53%) and diabetes (13%)
  - Hyperlipidemics (n=515): Hypertension (37%) and diabetes (9%)

Figure 1. Virologic Outcomes at Week 48 (FDA Snapshot)



- Switching to RPV/FTC/TAF was non-inferior to continuing RPV/FTC/TDF or EFV/FTC/TDF at Week 48 (Figure 1)
- Efficacy was comparable across age, sex, race, geographic regionsubgroups
- No emergent resistance mutations were detected in RPV/FTC/TAF participants

Adverse Events (AEs)

- After switching to RPV/FTC/TAF the rates of Grade 3/4 AEs in the age and sex sub-groups were low and comparable to the overall study population rates of 5.8% with RPV/FTC/TAF and 4.7% with (EFV or RPV) /FTC/TDF
- All study regimens were well tolerated with very low rates of discontinuation due to treatment-related AEs (≤2%)
- The only treatment-related AE leading to discontinuation occurring in more than 1 participant was fatigue (n=2; 0.3%) in the RPV/FTC/TAF arm
- Three RPV/FTC/TAF participants discontinued study drug for gastrointestinal AEs requiring proton pump inhibitor therapy
- There was 1 renal AE (decreased estimate glomerular filtration rate and 1 bone AE (traumatic fracture) leading to discontinuation in RPV/FTC/TAF participants and none in the comparator arms

Table 2. Bone Safety at Week 48

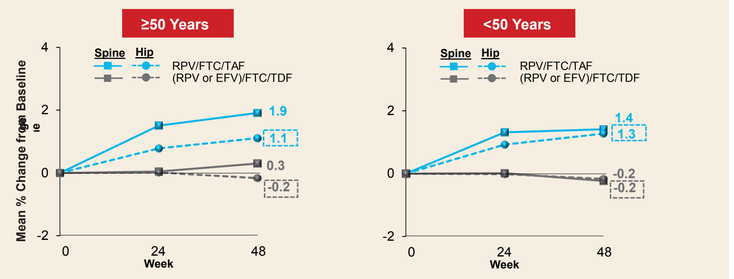
BMD Change (%) from Baseline to 48 Weeks

	1216			1160		
	RPV/FTC/ TAF	RPV/FTC/ TDF	P-value	RPV/FTC/ TAF	EFV/FTC/ TDF	P-value
Lumbar Spine (%)	+1.61	+0.08	<0.0001	+1.65	-0.05	<0.0001
Hip (%)	+1.04	-0.25	<0.0001	+1.28	-0.13	<0.0001

- Significant increases in spine and hip BMD observed at Week 48 after switching to RPV/FTC/TAF vs. continuing RPV/FTC/TDF or EFV/FTC/TDF (Table 2), as well as regardless of age and sex in pooled analyses (Figures 2 & 3)

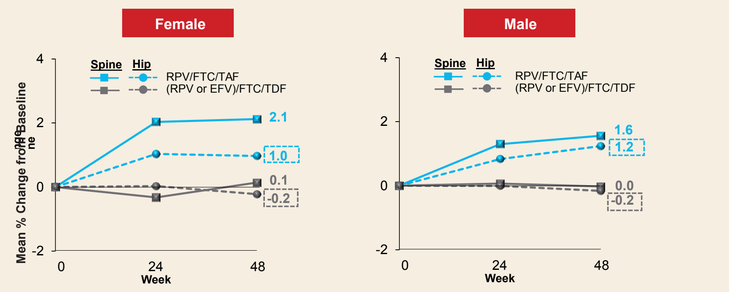
Results (continued)

Figure 2. BMD Changes by Age through Week 48



- Significant increases in spine and hip BMD observed at Week 48 after switching to RPV/FTC/TAF vs. continuing RPV/FTC/TDF or EFV/FTC/TDF regardless of age
  - Significant differences between arms at Weeks 24 and 48 for both spine and hip BMD (p<0.001)

Figure 3. BMD Changes by Sex through Week 48



- Significant increases in spine and hip BMD observed at Week 48 after switching to RPV/FTC/TAF vs. continuing RPV/FTC/TDF or EFV/FTC/TDF regardless of sex
  - Significant differences between arms at Weeks 24 and 48 (p≤0.001, except for hip in female at Week 24, p=0.005, and Week 48, p=0.018)

Bone Safety at Week 48

- Study 1216:
  - Only a subset of participants participated in BMD sub-study (n=357) compared to the 875 participants in Study 1160, thus BMD improvements/worsening are reported only for Study 1160
- Study 1160:
  - Baseline spine or hip osteoporosis was uncommon (<5%) and ~1/4 had osteopenia
  - Shifts between BMD categories (osteoporosis, osteopenia, and normal BMD) were statistically significant for spine (p<0.001) and hip (p=0.004) and favored TAF over TDF

Table 3. BMD Category Change from Baseline to 48 Weeks

TAF vs TDF, % (n/N)	Study 1160	
	Spine (n=369; n=389)	Hip (n=347; n=351)
Improvement: Osteoporosis to osteopenia	**35% vs 13%** (6/17) vs (2/16)	**0% vs 0%** (0/4) vs (0/4)
Improvement: Osteopenia to normal BMD	**22% vs 4%** (21/94) vs (4/91)	**13% vs 7%** (15/114) vs (9/123)
Worsening: Normal BMD to osteopenia	**3% vs 8%** (7/240) vs (20/262)	**0% vs 4%** (0/230) vs (10/240)
Worsening: Osteopenia to osteoporosis	**0% vs 1%** (0/94) vs (3/91)	**2% vs 1%** (2/114) vs (1/123)

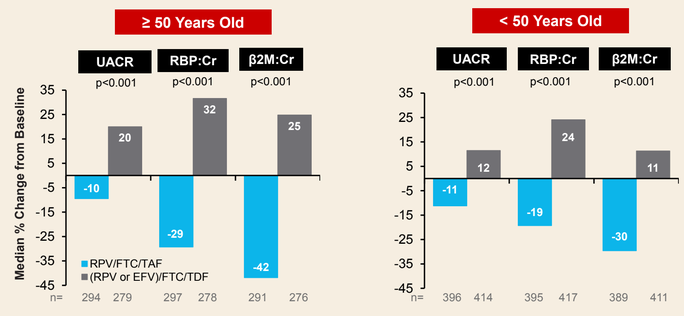
Renal Safety at Week 48

- There was 1 renal discontinuation with RPV/FTC/TAF and none in the comparator arms
  - 74-year old Black man with hypertension and screening eGFR of 54 mL/min experienced eGFR decrease to 47 mL/min at Week 37, and acutely to 26 mL/min a week later with no evidence of proteinuria or glycosuria
  - Study drug stopped as event deemed study drug related by the investigator
  - The next day, eGFR was 49 mL/min and EVG/COBI/FTC/TAF was started 1 week later and subsequent eGFR returned to baseline (52 mL/min)
- There were no cases of proximal renal tubulopathy or Fanconi Syndrome in any of the treatment arms
- Study 1216: Switching from RPV/FTC/TDF to RPV/FTC/TAF resulted in stable serum creatinine (SCr) (Table 4) and eGFR.
- Study 1160: Switching from EFV/FTC/TDF to RPV/FTC/TAF resulted in small SCr increase at Week 4 which remained stable from Week 12 to Week 48 (Table 4). This resulted in small eGFR changes (range: -5 to +3 mL/min) in the sub-groups which were not clinically relevant.
  - RPV's inhibition of tubular secretion of creatinine results in the observed small increases in serum creatinine concentrations without impacting actual glomerular filtration.
- Significant improvement in albuminuria and renal tubular markers (β2M:Cr and RBP:Cr), were observed at Week 48 after switching to RPV/FTC/TAF vs. continuing (RPV or EFV)/FTC/TDF
  - Improvements were seen in all sub-groups, regardless of age (≥ 50 or < 50), or pre-existing diabetes or hypertension (Figures 4-6)

Table 4. Median Serum Creatinine Changes (µmol/L) from Baseline to Week 48

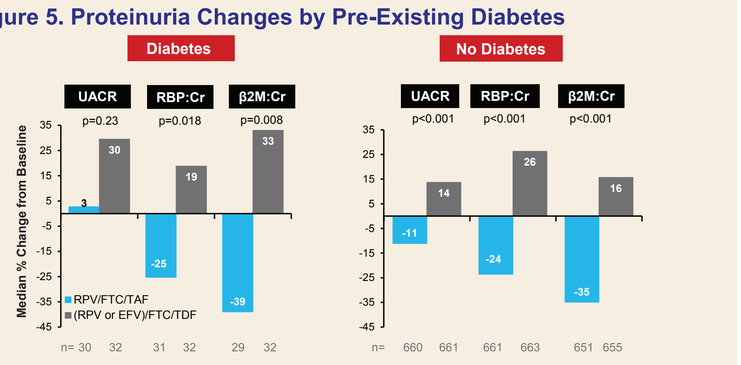
	1216			1160		
	RPV/FTC/ TAF	RPV/FTC/ TDF	P-value	RPV/FTC/ TAF	EFV/FTC/ TDF	P-value
Age						
≥ 50 years	-0.9	-0.9	0.86	5.3	0.0	<0.001
< 50 years	-2.7	-0.9	0.47	6.2	-0.9	<0.001
Pre-existing diabetes						
-yes	-3.5	3.5	0.81	0.9	-1.8	0.45
-no	-1.8	-0.9	0.70	6.2	0.0	<0.001
Pre-existing hypertension						
-yes	-2.7	-3.5	0.88	4.4	0.9	<0.001
-no	-0.9	-0.9	0.43	6.2	0.0	<0.001

Figure 4. Proteinuria Changes by Age*



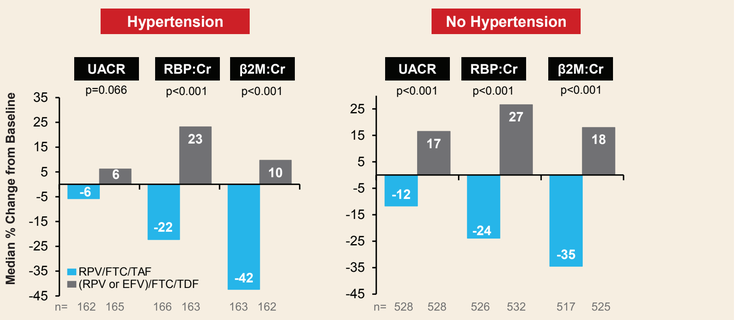
Cr: creatinine; β2M: beta-2 microglobulin; RBP: retinol-binding protein; UACR: urine albumin to creatinine ratio
* Significant differences between arms at Week 48 for the 3 measures at Week 48 timepoint (p<0.001)

Figure 5. Proteinuria Changes by Pre-Existing Diabetes



Cr: creatinine; β2M: beta-2 microglobulin; RBP: retinol-binding protein; UACR: urine albumin to creatinine ratio

Figure 6. Proteinuria Changes by Pre-Existing Hypertension

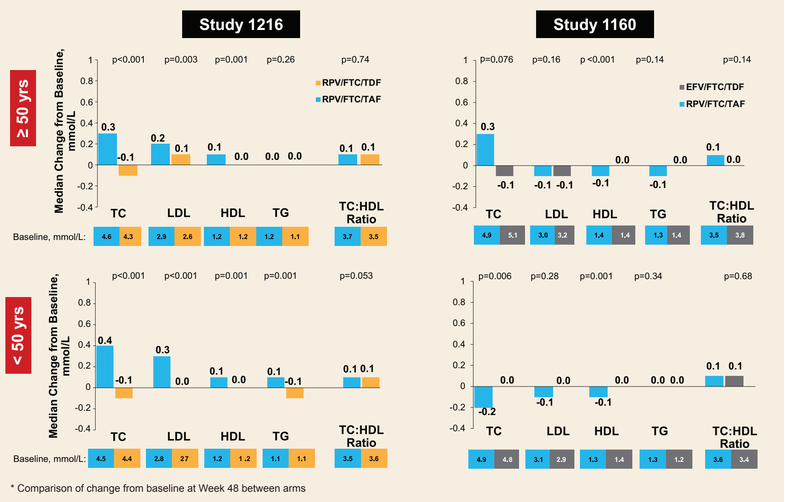


Cr: creatinine; β2M: beta-2 microglobulin; RBP: retinol-binding protein; UACR: urine albumin to creatinine ratio

Lipids at Week 48

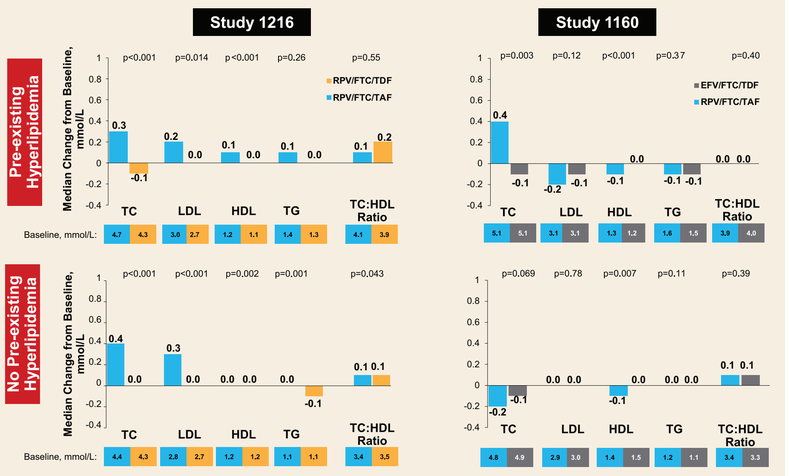
- Study 1216: Switching from RPV/FTC/TDF to RPV/FTC/TAF resulted in median increases ranging from 9 to 16 mg/dL for TC and LDL for sub-analyses by age and preexisting hyperlipidemia (Figure 7)
  - Participants with pre-existing hyperlipidemia, ≥ 50 years, and < 50 years: Similar changes in TC:HDL in both treatment groups (P=NS)
  - Participants without pre-existing hyperlipidemia: Difference in changes in TC:HDL between treatment groups were small (mean +0.2 vs +0.1, median +0.1 vs. +0.1; p=0.043)
- Study 1160: Switching from EFV/FTC/TDF to RPV/FTC/TAF resulted in decreases in all 4 lipid parameters, irrespective of age or preexisting hyperlipidemia (Figure 8)
  - Changes in TC:HDL ratio were similar for both arms, irrespective of age or preexisting hyperlipidemia (P=NS)
- Use of lipid modifying medications (i.e., statins) was low (4%) when switching to RPV/FTC/TAF from either (RPV or EFV)/FTC/TDF

Figure 7. Fasting Lipids at Week 48: Change from Baseline*



* Comparison of change from baseline at Week 48 between arms

Figure 8. Fasting Lipids at Week 48: Change from Baseline*



* Comparison of change from baseline at Week 48 between arms

Conclusions

- Through 48 weeks, virologically suppressed patients switching to RPV/FTC/TAF maintained high suppression rates.
- Compared to remaining on EFV/FTC/TDF or RPV/FTC/TDF, RPV/FTC/TAF adults ≥ 50 years, women, and those with diabetes or hypertension demonstrated improved bone and/or renal (proteinuria and tubular function) measures
- In participants with pre-existing hyperlipidemia and those ≥ 50 years, median changes in the TC:HDL ratios were similar between treatment groups.
- Generally, the benefits observed in the subgroups of interest appear similar to the overall study populations
- These findings are of particular importance as individuals living with HIV age and experience medical co-morbidities that put them at higher risk of renal and bone disease.

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