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An RCT of Rilpivirine vs Efavirenz on Cardiovascular Risk in Healthy Volunteers

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Introduction

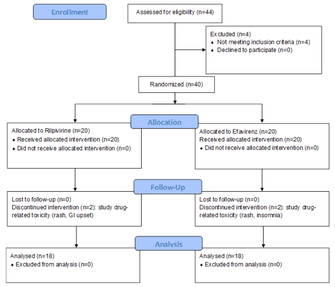
· We have recently demonstrated that efavirenz, an NNRTI, may impair endothelial function in HIV-infected patients. EFV has also been linked to lipid abnormalities and oxidative stress.
· Long-acting rilpivirine (RPV), an injectable NNRTI, is undergoing evaluation as an agent to be used as pre-exposure prophylaxis in uninfected persons.
· However, it is unknown if RPV has a similar CVD risk profile as EFV.
· Thus, we sought to compare the effects between RPV and EFV in a healthy, HIV-uninfected population.

Methods

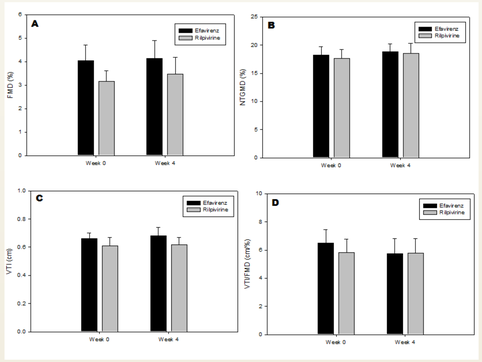
· We performed a prospective, randomized (1:1) open-label trial in 40 HIV-uninfected healthy volunteers (ClinicalTrials.gov NCT01585038).
· Vascular indices [flow-mediated dilation (FMD), nitroglycerin-mediated dilation (NTGMD), hyperemic velocity-time integral (VTI), FMD/VTI of the brachial artery], metabolic parameters, inflammatory markers, and oxidative stress were measured before and after 4 weeks of study drug treatment. The vascular measures were blinded to the reader (S.K.G.).
· Key inclusion criteria included: ≥ 18 years of age; negative screening for HIV, HBVsAg, HCV Ab; no history of psychiatric disorders.
· Key exclusion criteria included: pregnancy/breastfeeding; history of cardiovascular disease; active tobacco use; screening glucose ≥ 200mg/dL, total cholesterol >260mg/dL, CrCl <55mL/min, or PHQ-9 depression score ≥ 10.
· P <0.05 considered statistically significant.

Results

Flow of Participants



Changes in Vascular Imaging Parameters



Vascular indices at Week 0 (Entry) and at Week 4. There were no significant differences between groups in flow-mediated dilation (FMD), nitroglycerin-mediated dilation (NTGMD), reactive hyperemic velocity-time integral (VTI), or VTI/FMD. Vertical bars represent absolute values at each time point with upper whisker as the standard error.

Baseline Characteristics

Characteristic	Efavirenz (n=20)	Rilpivirine (n=20)	P-value
Age (years)	30.4 (20.3, 54.5)	35.5 (20.4, 66.3)	0.41
Gender			
Female	15 (75%)	10 (50%)	0.19
Male	5 (25%)	10 (50%)	
Race			
Black	6 (30%)	9 (45%)	0.51
Non-Black	14 (70%)	11 (55%)	
Previous tobacco use	6 (30%)	10 (45%)	0.33
Body mass index, kg/m^2	29.5 (19.4, 46.1)	24.7 (17.5, 38.9)	0.10

Data presented as median (min, max) or as frequency (%).

Four-week Changes in Circulating Biomarkers of Oxidative Stress, Inflammation, and Metabolism

Biomarker	Efavirenz	Rilpivirine	Mean difference	P-value
F2-isoprostanes, pg/mL	92.7 (178.6) (n=14)	-101.4 (215.7) (n=12)	194.1 (34.6, 353.7)	0.02
hsCRP, mg/L	0.80 (2.47)	-0.41 (6.01)	1.21 (-2.30, 4.71)	0.35
IL-6, pg/mL	1.93 (5.63)	0.09 (2.51)	1.84 (-1.46, 5.14)	0.21
sVCAM-1, pg/mL	-27.62 (125.20)	-20.92 (68.95)	-6.70 (-75.89, 62.49)	0.41
Total cholesterol, mg/dL	19.39 (23.90)	-5.78 (16.45)	25.17 (11.27, 39.06)	<0.01
LDL-C, mg/dL	13.29 (19.50)	-2.24 (13.43)	15.54 (4.20, 26.88)	<0.01
HDL-C, mg/dL	2.17 (10.35)	-1.28 (9.53)	3.44 (-3.30, 10.18)	0.31
Total cholesterol/HDL-C	0.29 (0.48)	-0.05 (0.49)	0.35 (0.02, 0.67)	0.04
Triglycerides, mg/dL	19.00 (62.11)	-10.11 (31.79)	29.11 (-4.74, 62.96)	0.11
HOMA-IR	-0.43 (1.50)	0.60 (1.62)	-1.03 (-2.08, 0.03)	0.06

Data presented as mean (SD) or as mean (95% CI).

Results

· We also examined changes in bilirubin levels as bilirubin may have antioxidant properties. We found significant reductions in total bilirubin levels with EFV compared to RPV [mean (95% CI) difference -0.169 (-0.309, -0.030) mg/dL; (P=0.019)].
· However, the changes in total bilirubin levels did not correlate with changes in F2-isoprostane levels in the total group or in either of the individual study groups.
· We did not find appreciable changes in serum creatinine in either the EFV [0.005 (0.046) mg/dL] or RPV [0.008 (0.101) mg/dL] groups with no significant difference between the two groups [mean (95% CI) difference, -0.003 (-0.058, 0.052); P=0.91].
· There were 65 total adverse events (either Grade 1 or 2), with 39 in the EFV arm and 26 in the RPV arm (P>0.2). There were no Grade 3 or 4 toxicities and no serious adverse events.

Conclusions

·There were no significant differences between RPV and EFV on any vascular measure, marker of inflammation, or safety in HIV-uninfected, healthy volunteers.
· EFV led to significant increases over 4 weeks in total cholesterol, LDL-C, TC/HDL-C, and F2-isoprostanes compared to RPV.
· Strengths of the trial included its randomized allocation and inclusion of a diverse group of healthy volunteers. The use of uninfected participants precluded confounding of the results by HIV infection itself and provided an analysis in those who might use these agents as PrEP.
· The study was limited by the open-label design, relatively small sample size, and the short duration of drug exposure.
· Compared to EFV, RPV may be a safer choice for PrEP in regards to potential lipid and oxidative stress associated complications, although longer-term studies are required for confirmation.

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