A pilot 24-week open-label randomized controlled clinical trial to assess the safety, tolerability and efficacy of dual therapy with raltegravir/lamivudine (RAL/3TC) combination when replacing standard combination therapy in HIV-Infected patients with prolonged viral suppression: the RALAM Study.

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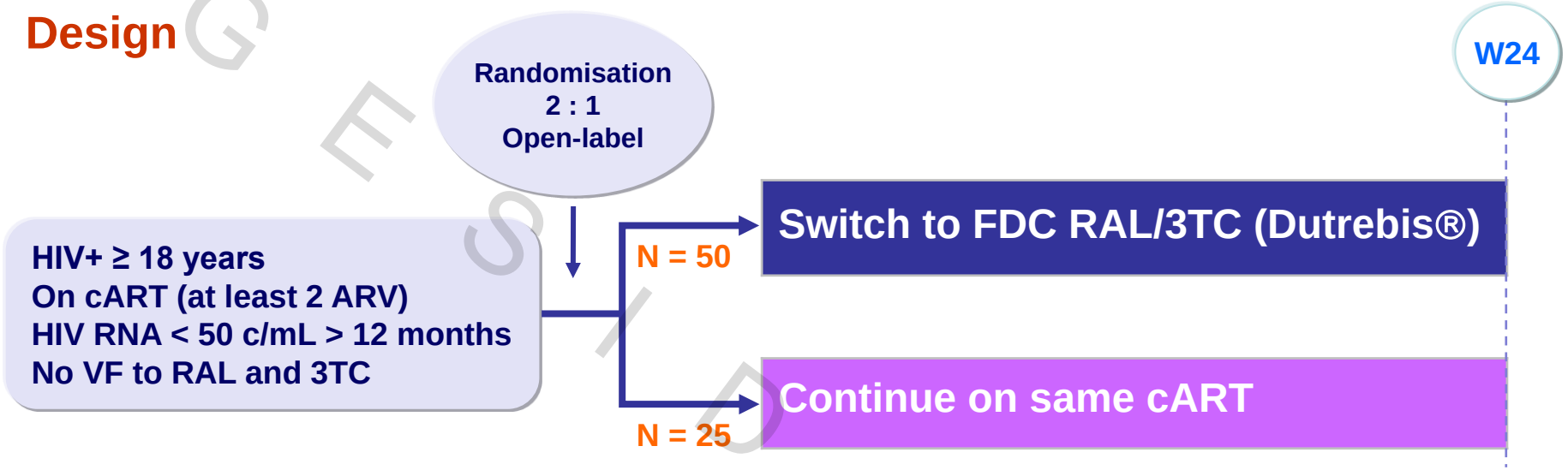
Background

- Although triple therapy is the gold standard in antiretroviral-naïve patients, dual combinations including an integrase inhibitor plus a non-nucleoside reverse transcriptase inhibitor have also shown non-inferior efficacy in randomized clinical trials (dolutegravir+rilpivirine, SWORD study; cabotegravir+rilpivirine, LATTE-2) or very favorable results in observational studies (raltegravir+etravirine, ETRAL study) in virologically suppressed patients.
- Maintenance therapy with dolutegravir+lamivudine has shown promising results in some observational studies and randomized clinical trials are ongoing. There is no data on the dual combination raltegravir+lamivudine.
- A fixed-dose combination containing 300 mg raltegravir (RAL)/150 mg lamivudine (3TC) BID has been approved by FDA and EMA.
- We hypothesized that switching to RAL/3TC in patients with viral suppression would maintain efficacy and be well tolerated.

Methods

- **Design**



- **Endpoints**

- Primary end-point: Patients with therapeutic failure (defined as viral failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death) at week 24.

- Secondary end-points: Changes in laboratory (glucose, HOMA, lipids, estimated glomerular filtration rate, urine beta-2-microglobulin, plasma vitamin D, blood cells, CD4 and CD8 cells), body composition (DXA scan), sleep quality (Pittsburgh Sleep Quality Index), and adherence (Morisky-Green test), and overall and severe adverse events. Also, ultrasensitive HIV-1 RNA and HIV reservoir not presented here.

Safety & Efficacy of Dual Therapy With Raltegravir/Lamivudine (RALAM). ClinTrials.gov NCT02284035

Statistical methods

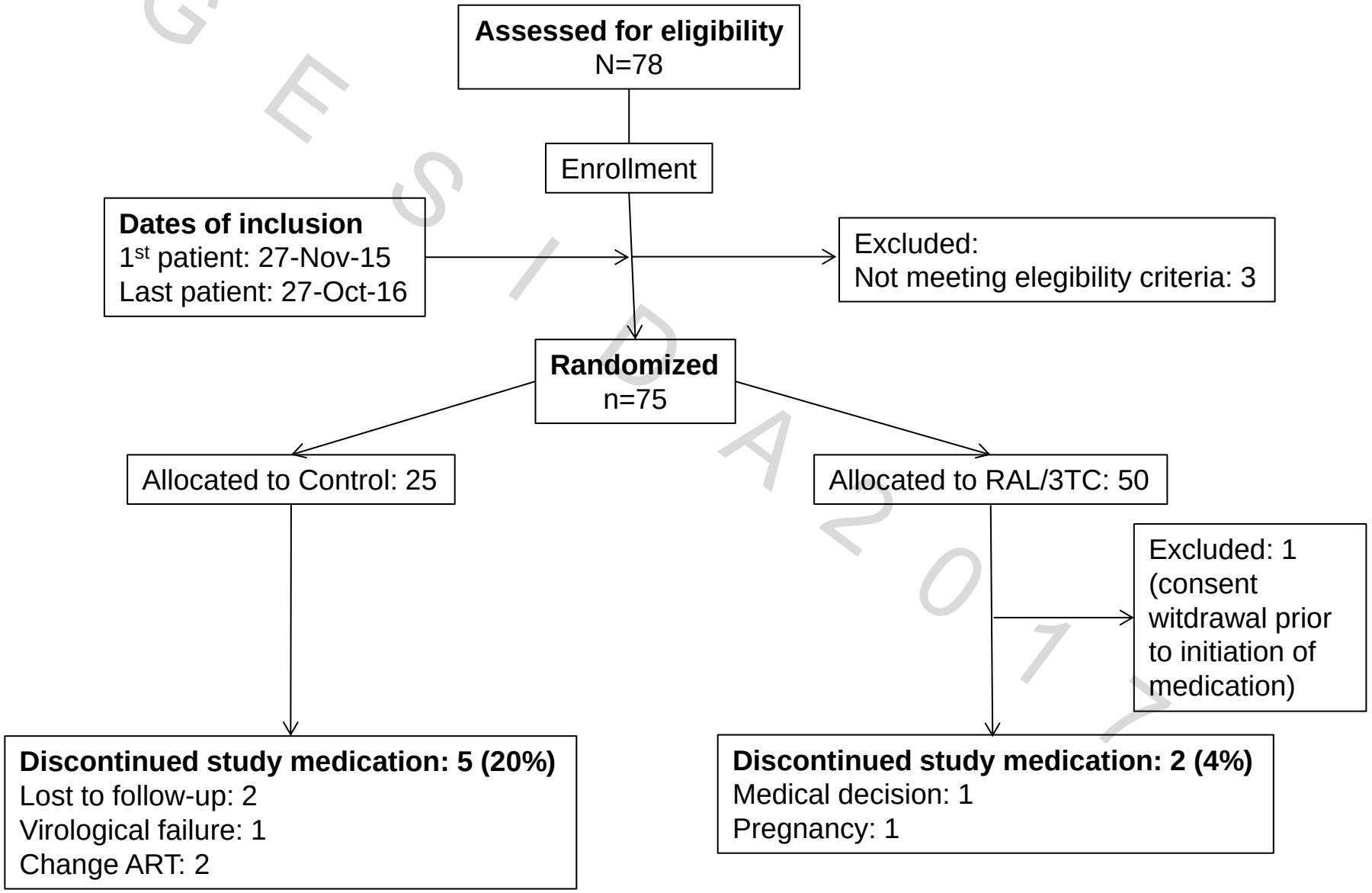
- Analysis of the primary endpoint was performed on both ITT and per protocol populations. Change over time in continuous variables in each arm were calculated as DID estimator (Difference in differences estimator based on linear regression model with time, group and time-group interaction).

- **Sample size:** We assumed that the true difference in efficacy between the treatment arms is zero and that the overall response rate is 95% at week 24. A total of 60 patients (30 per arm) is required to provide 80% power to demonstrate non-inferior efficacy for the experimental arm, compared to the control arm, with a one-sided significance level of 2.5% and a non-inferiority margin (delta) of -26%. Finally, a non-balanced design with a ratio of 2:1 was chosen increasing the total sample to 75 patients.

- DSMB would review the data if 4 episodes of treatment failure were detected and subsequently every 4 new episodes of treatment failure. Study would be interrupted as soon as 5 episodes (10%) of confirmed virological failure were detected in the experimental arm.

- This pilot study is exploratory, and must serve to see whether the strategy is feasible, if the results are good enough, to design a larger well-powered study.

Patients disposition



Baseline characteristics (1)

	Control (n=25)	RAL/3TC (n=49)	Total (n=74)	P-value
Age, years	50 (13)	50 (12)	50 (12)	0.9397
Men (%)	21 (84)	37 (76)	58 (78)	0.4014
Prior ART Backbone				
TDF-containing	17	26	43	
ABC-containing	8	22	30	
Nuke-sparing	-	1	1	
Prior ART 3rd Drug				
PI	3	8*	11	
NNRTI	16	29*	45	
INSTR	5	13	19	
NRTI	1	-	1	

Data are mean (SD) unles otherwise stated
* One patient allocated at Control arm was taking DRV/cobi + RAL

Baseline characteristics (2)

	Control (n=25)	RAL/3TC (n=49)	Total (n=74)	P-value
PSQI score, median (IQR)	4 (3; 9)	5 (4; 9)	4.5 (3; 9)	0.6625
Adherence, Morisky, median (IQR)	19 (18.5; 20)	19 (18; 20)	19 (18; 20)	0.4889
CD4 cells/mm^2	564 (240)	655 (295)	622 (277)	0.1824
CD8 cells/mm^2	798 (340)	767 (342)	777 (339)	0.7207
Creatinine, mg/dL	0.84 (0.18)	0.85 (0.20)	0.85 (0.19)	0.7833
eGFR <90 mL/min, CKD EPI	10 (40)	16 (33)	36 (35)	0.5312
Triglycerides, mg/dL	112 (53)	99 (50)	103 (51)	0.2971
Total cholesterol, mg/dL	187 (44)	189 (46)	188 (45)	0.8873
LDL cholesterol, mg/dL	115 (29)	120 (39)	118 (36)	0.6679
HDL cholesterol, mg/dL	46 (13)	48 (15)	47 (14)	0.4450
Glucose, mg/dL	96 (13)	96 (12)	96 (12)	0.9603
Insulin, U/L	16 (16)	14 (10)	14 (12)	0.5077
25OH Vitamin D, ng/mL	17 (10)	17 (9)	17 (9)	0.7786
Urine beta-2 microglobulin, mg/g	595 (949)	673 (773)	651 (814)	0.8298

Data are mean (SD) unles otherwise stated
PSQI: Pittsburg Sleep Quality Index

Baseline characteristics (3)

	Control (n=25)	RAL/3TC (n=49)	Total (n=74)	P-value
BMI, kg/m^2 (mean, SD)	26 (4)	25 (4)	25 (4)	0.4274
Fat (DXA)				
Trunk fat, grams	9891 (8052; 12611)	9232 (6587; 12976)	9738 (7140; 12976)	0.5485
Trunk fat, %	30 (24; 33)	30 (22; 36)	30 (22; 36)	0.9271
Upper limbs fat, grams	1950 (1538; 2765)	2420 (1370; 2920)	2290 (1508; 2912)	0.5156
Upper limbs fat, %	22 (19; 36)	29 (19; 35)	28 (19; 36)	0.4269
Lower limbs fat, grams	5375 (3156; 9577)	5736 (4094; 7658)	5649 (3918; 8349)	0.9424
Lower limbs fat, %	26 (15; 37)	27 (20; 32)	27 (19; 34)	0.5674
Total body fat, grams	65121 (25318; 74254)	52389 (21558; 66220)	55347 (21558; 70334)	0.4450
Total body fat, %	25 (21; 33)	29 (22; 33)	28 (21; 33)	0.5921
Bone (DXA)				
Femur T-score (mean, SD)	-0.63	-1.04 (0.88)	-0.90 (0.86)	0.0479
Lumbar spine T-score (mean, SD)	-0.54 (1.08)	-0.92 (1.16)	-0.79 (1.14)	0.1709

Data are median (IQR) unles otherwise stated

Therapeutic failure at week 24: ITT analysis

Final status at 24 weeks ITT	Control (n=25)	RAL/3TC (n=49)	Total (n=74)
Study completed	20 (80%)	47 (96%)	67 (91%)
Lost to follow-up	2 (8%)	0 (0%)	2 (3%)
Pregnancy	0 (0%)	1 (2%)	1 (1%)
Medical decision	0 (0%)	1 (2%)	1 (1%)
Virological failure	1 (4%)	0 (0%)	1 (1%)
ART change	2 (8%)	0 (0%)	2 (3%)

Proportion of therapeutic failures at 24 weeks		
Proportion RAL/3TC	Proportion Control	**Difference in propostions (95% CI) (RAL/3TC) - Control**
0.041	0.200	**-0.159 (-0.353; -0.012)**

We can claim that RAL/3TC is not inferior to Control since the upper bound of the confidence interval -0.012 for the difference in proportions does not cross over the pre-specified noninferiority margin, δ (0.26).

As an exploratory *post-hoc* analysis, not planned in the protocol, superiority test is performed:

Therapeutic failure	Control (n=25)	RAL/3TC (n=49)	Total (n=74)	P-Value
No	20 (80%)	47 (96%)	67 (91%)	0.0398
Yes	5 (20%)	2 (4%)	7 (9%)	

Therapeutic failure at week 24: OT analysis

Final status at 24 weeks OT	Control (n=23)	RAL/3TC (n=48)	Total (n=74)
Study completed	20 (80%)	47 (96%)	67 (91%)
Medical decision	0 (0%)	1 (2%)	1 (1%)
Virological failure	1 (4%)	0 (0%)	1 (1%)
ART change	2 (8%)	0 (0%)	2 (3%)

Proportion of therapeutic failures at 24 weeks		
Proportion RAL/3TC	Proportion Control	**Difference in propostions (95% CI) (RAL/3TC) - Control**
0.021	0.130	**-0.110 (-0.301; 0.013)**

We can claim that RAL/3TC is not inferior to Control since the upper bound of the confidence interval -0.012 for the difference in proportions does not cross over the pre-specified noninferiority margin, δ (0.26).

Change in laboratory parametres

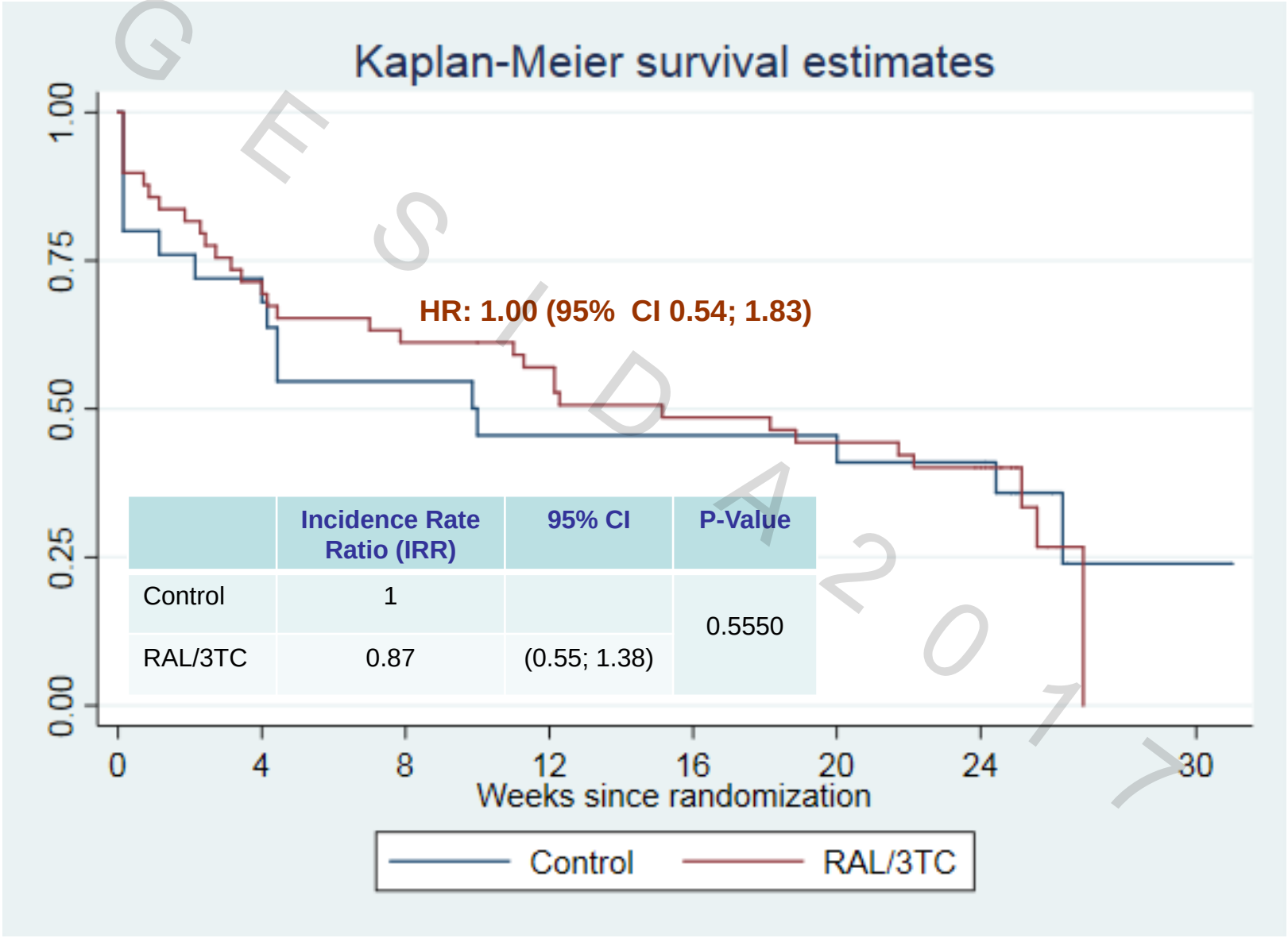
	Change in Control (n=25)	Change in RAL/3TC (n=49)	Change in RAL/3TC vs. Change in Control	P-value
PSQI score	1.088 (0.714; 1.658)	0.957 (0.716; 1.280)	0.880 (0.528; 1.468)	0.6243
Adherence, Morisky	3.309 (0.903; 12.130)	1.074 (0.471; 2.449)	0.325 (0.070; 1.512)	0.1517
CD4 cells/mm^2	0.990 (0.762; 1.287)	0.972 (0.816; 1.157)	0.981 (0.716; 1.344)	0.9054
CD8 cells/mm^2	0.867 (0.664; 1.133)	0.905 (0.757; 1.081)	1.043 (0.757; 1.438)	0.7965
Creatinine, mg/dL	1.042 (0.912; 1.190)	0.977 (0.894; 1.068)	0.938 (0.799; 1.101)	0.4318
eGFR <90 mL/min, CKD EPI	1.268 (0.529; 3.041)	0.917 (0.273; 3.081)	0.723 (0.162; 3.226)	0.6705
Triglycerides, mg/dL	0.901 (0.681; 1.191)	0.992 (0.822; 1.196)	1.101 (0.787; 1.541)	0.5744
Total cholesterol, mg/dL	-1.280 (-27.798; 25238)	0.803 (-16.986; 18.593)	2.083 (-29.849; 34.016)	0.8983
LDL cholesterol, mg/dL	2.222 (-20.663; 25.108)	-0.611 (-16.103; 14.881)	-2.834 (-30.469; 24.802)	0.8407
HDL cholesterol, mg/dL	-0.099 (-8.578; 8.380)	1.158 (-4.530; 6.845)	1.257 (-8.953; 11.466)	0.8094
Glucose, mg/dL	0.970 (0.878; 1.072)	0.922 (0.862; 0.986)	0.950 (0.843; 1.071)	0.4046
Insulin, U/L	0.866 (0.571; 1.313)	0.896 (0.666; 1.206)	1.035 (0.621; 1.727)	0.8938
25OH Vitamin D, ng/mL	1.762 (1.246; 2.490)	1.526 (1.201; 1.938)	0.866 (0.569; 1.319)	0.5034
Urine beta-2 microglobulin, mg/g	1.325 (0.278; 6.318)	0.410 (0.149; 1.123)	0.309 (0.048; 1.986)	0.2162

PSQI: Pittsburg Sleep Quality Index

Change in body composition parametres

	Change in Control (n=25)	Change in RAL/3TC (n=49)	Change in RAL/3TC vs. Change in Control	P-value
Fat (DXA)				
Total body fat, grams	-27023 (-60148; 6103)	5094 (-18191; 28378)	32116 (-8374; 72606)	0.1200
Trunk fat, grams	882 (-2399; 4163)	196 (-2062; 2454)	-686 (-4669; 3297)	0.7358
Bone (DXA)				
Femur T-score	0.153 (-0.369; 0.675)	-0.066 (-0.425; 0.293)	-0.219 (-0.853; 0.415)	0.4981
Lumbar spine T-score	0.115 (-0.553; 0.783)	0.087 (-0.373; 0.547)	-0.028 (-0.840; 0.783)	0.9455

Adverse events: Incidence



	Incidence Rate Ratio (IRR)	95% CI	P-Value
Control	1		0.5550
RAL/3TC	0.87	(0.55; 1.38)	

Adverse events: Profile

	Control (n=25)	RAL/3TC (n=49)	Total (n=74)
Systemic	2 (8%)	-	2 (2%=
Infection	6 (23%)	12 (21%)	18 (22%)
Dermatologic	2 (8%)	2 (4%)	4 (5%)
Cardiovascular	-	1 (2%)	1 (1%)
Gastrointestinal	2 (8%)	16 (28%)	18 (22%)
Neurologic	4 (15%)	5 (9%)	9 (11%)
Muscular	5 (19%)	14 (25%)	19 (23%)
Genitourinary	-	1 (2)	1 (1%)
Ophtalmologic	-	3 (5%)	3 (4%)
Laboratory	5 (19%)	3 (5%)	8 (10%)
TOTAL	26 (100%)	57 (100%)	83 (100%)

Conclusions

- This pilot study suggests that switching to RAL/3TC in patients with viral suppression maintains efficacy and is well tolerated.

- These results support the viability of a well-powered randomized trial.